Exploring Flow Chemistry for the Synthesis and Scale-up of Small Organic Molecules

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Exploring Flow Chemistry for the Synthesis and Scale-up of Small Organic Molecules

A thesis submitted for the partial fulfilment of the requirement for the

Degree of

Doctor of Philosophy

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By

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Durham

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Appendix

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Materials and Methods

Chemicals: The chemicals used were obtained from the companies Sigma-Aldrich / Fluka, Alfa Aesar, TCI or Fluorochem and were used without further purification.

Chromatography: For the TLC chromatography Merck TLC Aluminium oxide 60 F254 with glass backing were used. Detection was carried out either by UV absorption or by treatment of the plate with an acidic solution of potassium permanganate and drying using a hand held hot-air dryer.

NMR-Spectroscopy: The NMR spectra were recorded on a Bruker Avance-400 and Varian VNMRS-700 spectrometer in the indicated solvent at a temperature of 297 K. Commercially available deuterated chloroform, methanol or DMSO was used as a solvent. The spectra were always set to the reference value of the solvent, for example chloroform (for ^{1}H-NMR spectra to 7.26 ppm and for ^{13}C-NMR spectra to 77.00 ppm). For the exact analysis and assignment of the signals in more complex compounds, COSY, HSQC and HMBC spectra were additionally added. Chemical shifts were reported in ppm and coupling constants J in hertz (Hz). The following abbreviations were used for the multiplicities of the signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

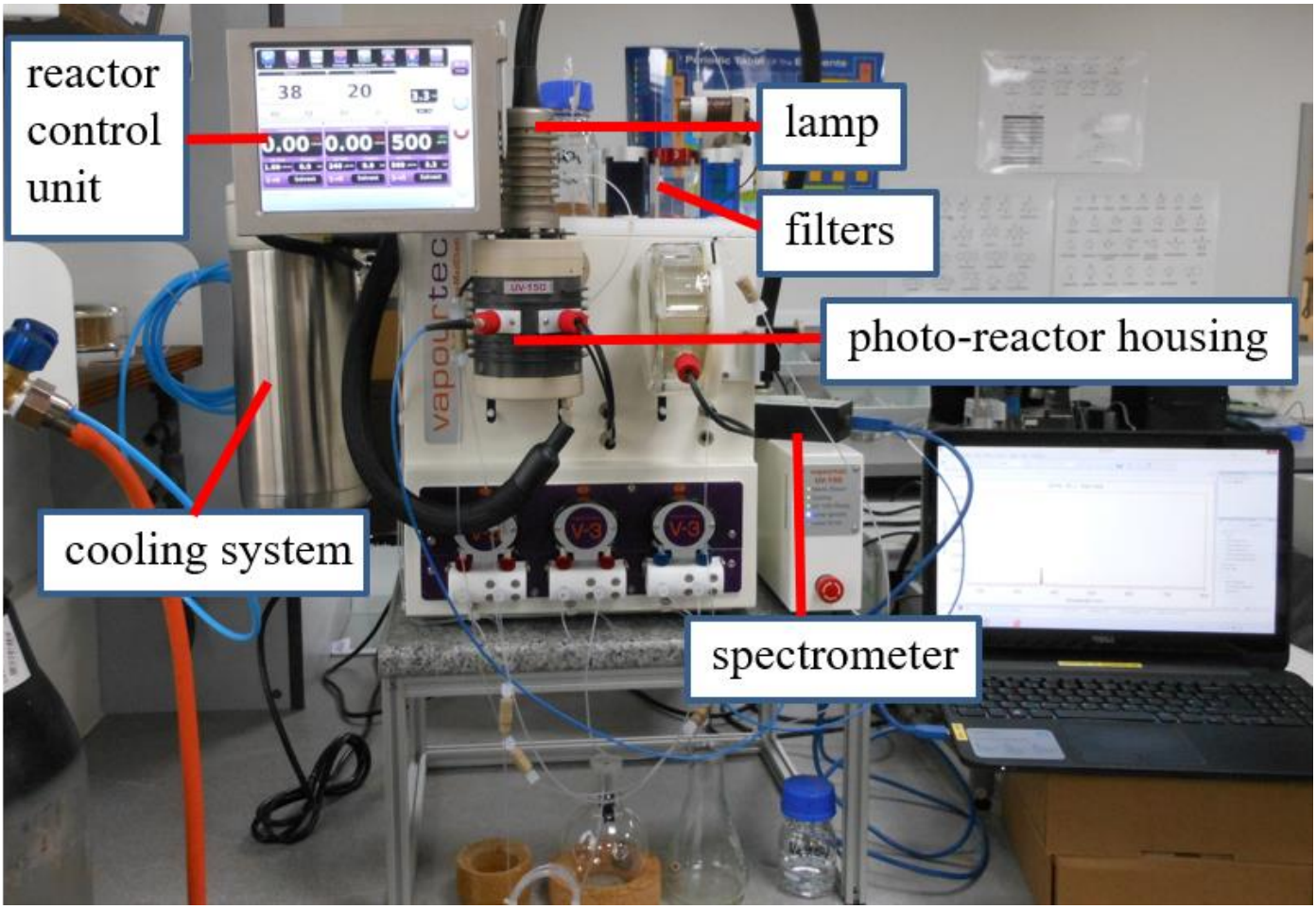
MS-Spectroscopy: GCMS spectra were obtained using an Agilent 6890N gas chromatograph coupled with an Agilent 5973 inert mass selective detector operating in EI mode with a custom-built Anature auto sampler/injector or by Durham University Mass Spectrometry service. Electrospray (ES) mass spectra were obtained using a TQD mass spectrometer (Waters UK, Ltd; all were obtained by Durham University Mass Spectrometry service.

IR-Spectroscopy: The infrared spectra were recorded with a PerkinElmer Spectrum One IR spectrometer. The samples were measured by the ATR method (attenuated total reflection). The evaluation was limited to the bands characteristic of the compound. The position of the absorption bands in the IR spectrum was expressed in wave numbers $\tilde{\nu}$ (cm^{-1}).

Melting point determination: The melting point was determined using an Electrothermal 9100 capillary melting point device. The melting point range was recorded for the determination of melting points for resinous solids.

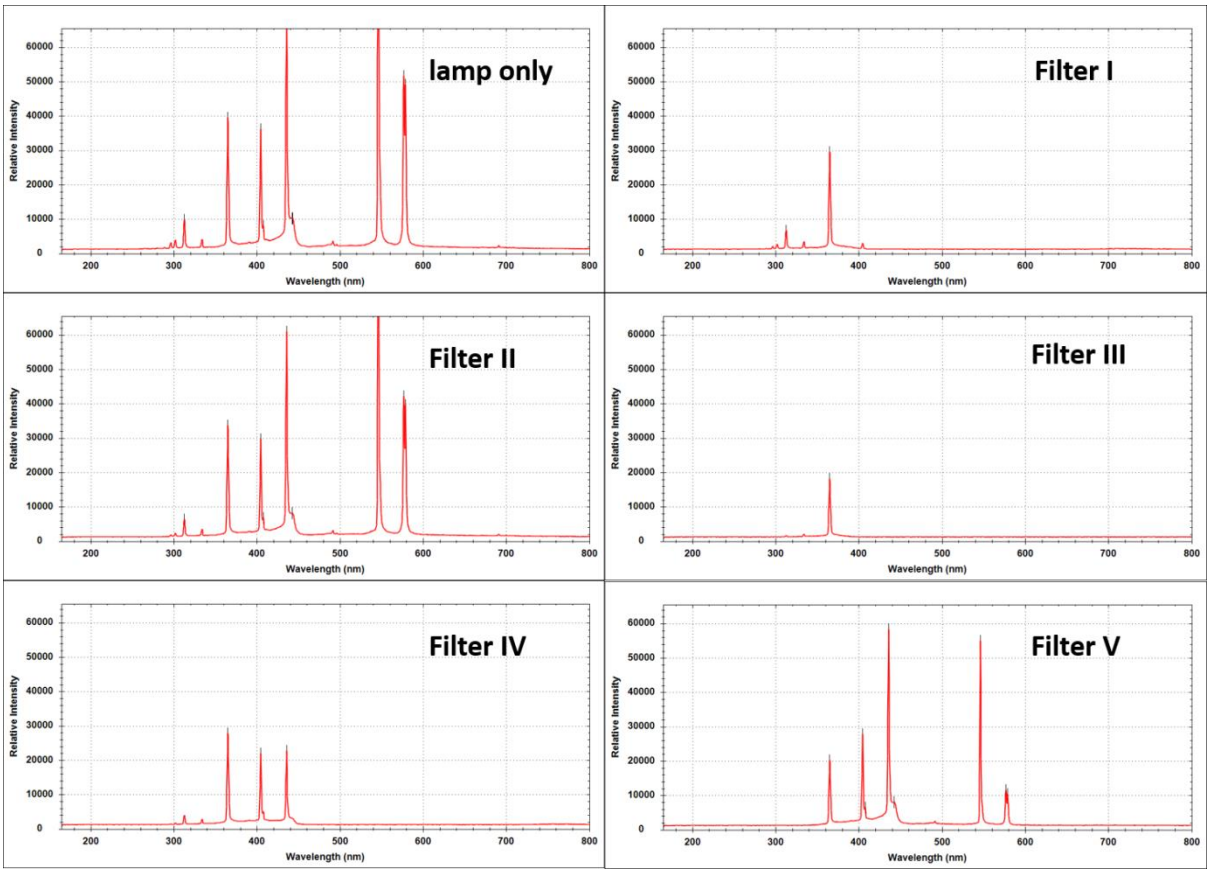
Photo-reactor set-up:

For performing all of the reactions a commercially available Vapourtec E-series system comprising of three peristaltic pumps and a UV-150 photo-reactor was used. Temperature control of the photo-reactor was achieved via an attached Dewar filled with solid CO_2 and attached to a N_2-cylinder (see image below). The photochemical reactions were monitored via a portable ExemplarLS spectrometer providing information through continuous recording of emission/transmission spectra. Different filters (see next page for details) were used and placed in between the high intensity medium pressure lamp and the reactor coil (FEP 10 mL volume).



Emission spectra of different filters used

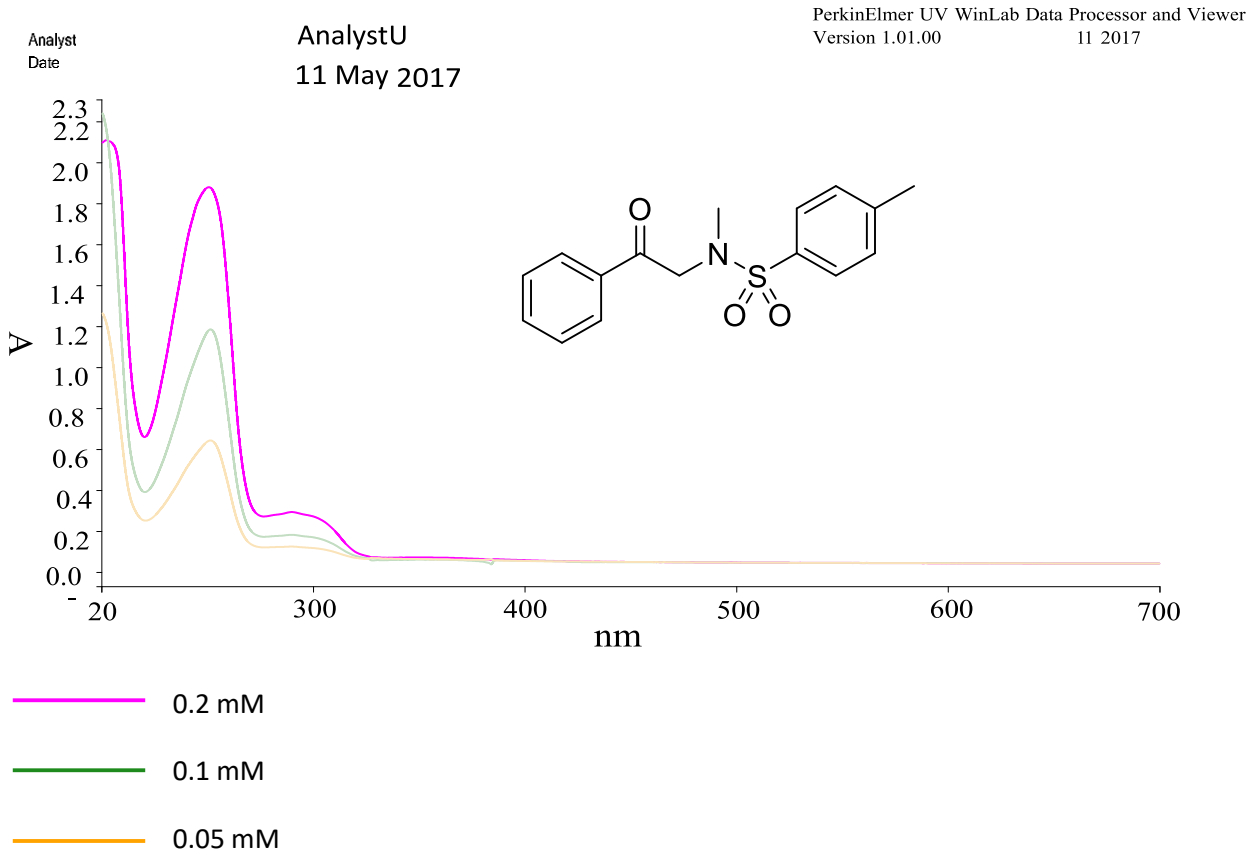
Shown below are the emission spectra recorded for various filters using water as solvent at 50% lamp power setting (80 W) using a portable ExemplarLS spectrometer. For the reaction performed in this work was used a medium pressure mercury lamp 150 W at 100% power fitted with the gold wavelength filter selector (λ= 415-220 nm transmission).



Photochemical flow synthesis of 3-hydroxyazetidines

UV-Vis recording of spectra.

The UV-Vis spectrum of compounds **1a**, **2a**, **6a**, **16a** and **18a**.



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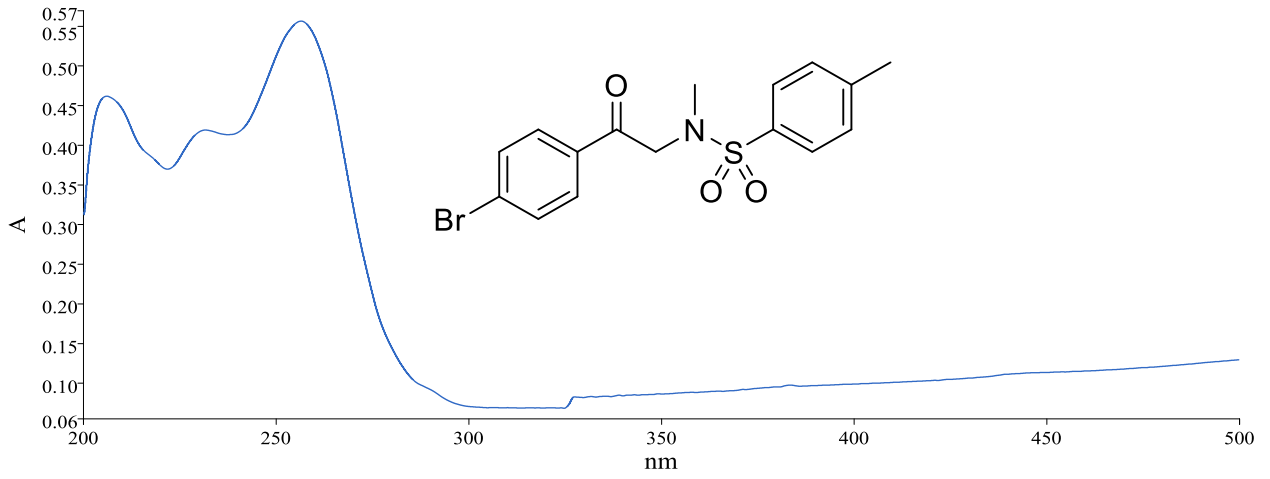

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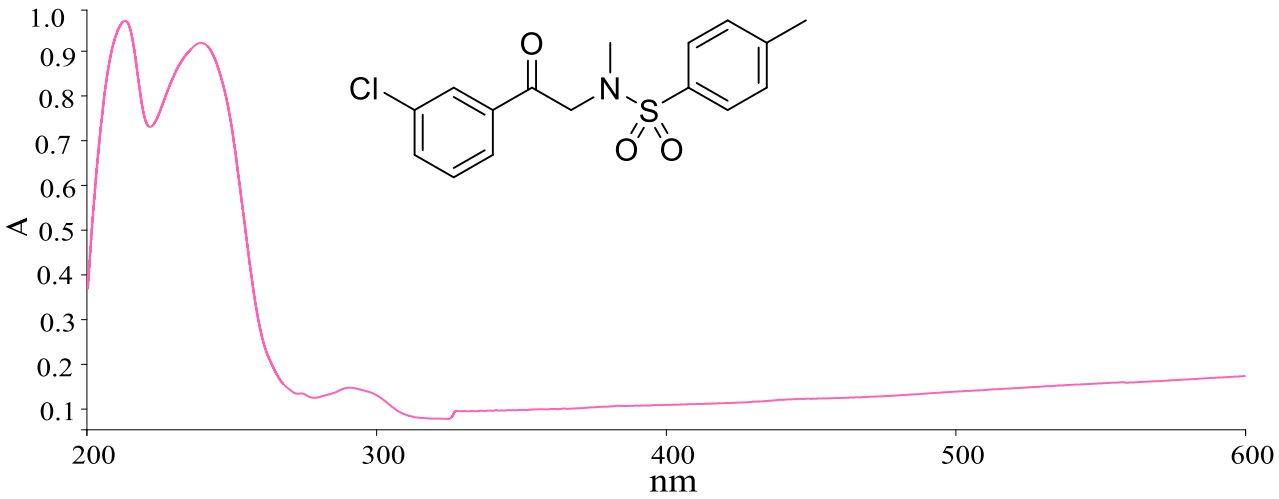

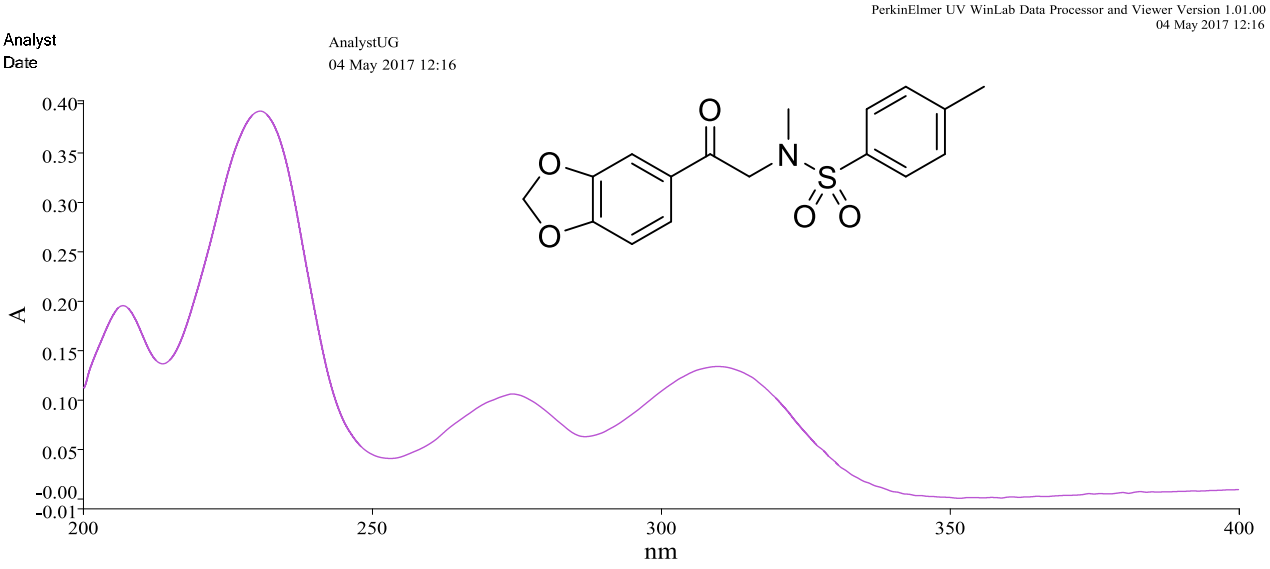
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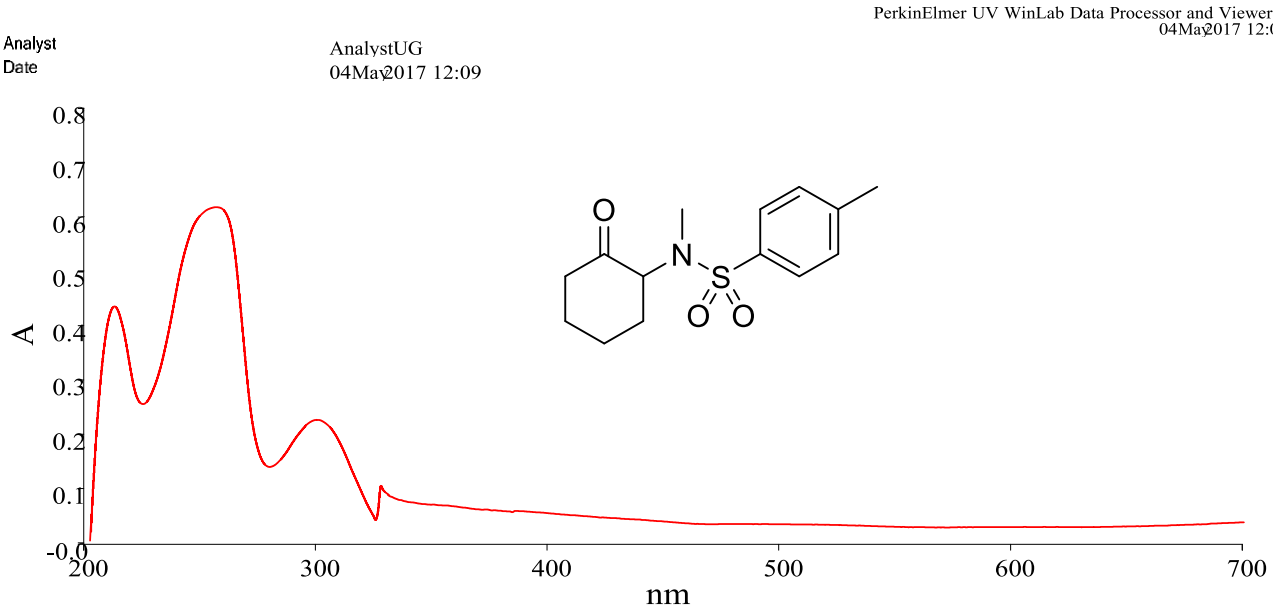
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400
500
600
700
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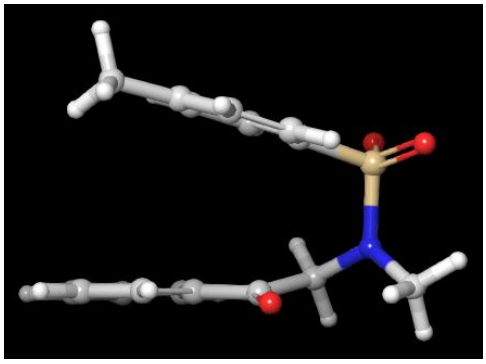
N
S
O
O

5. Molecular conformation modelling

Unsubstituted (H):



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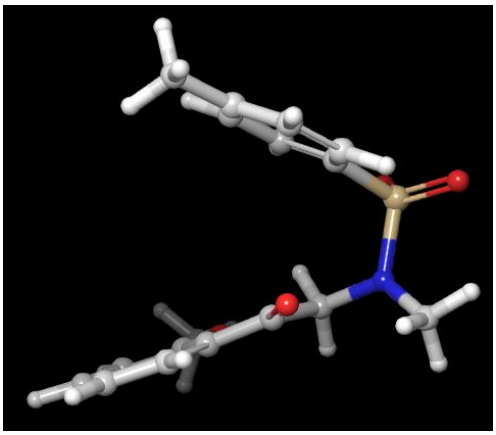
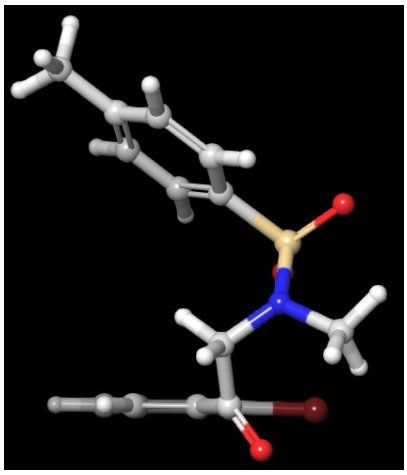
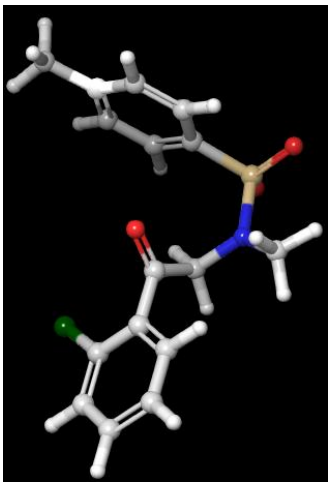
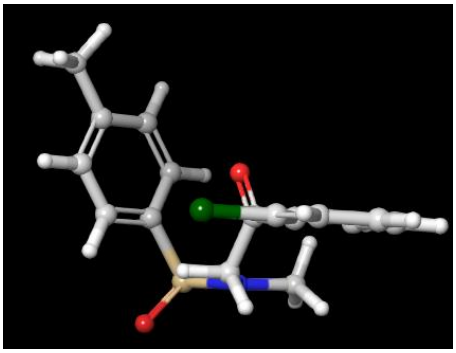


Ortho-Br:



Orto-Cl:





Ortho-Me:

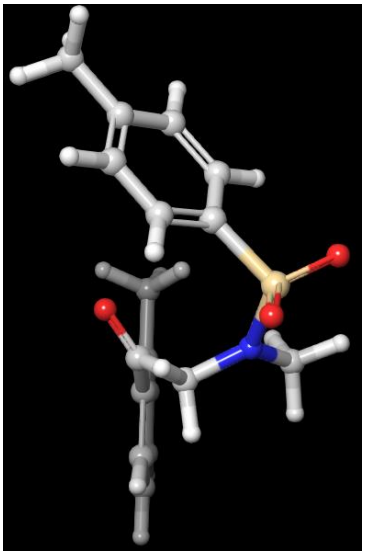


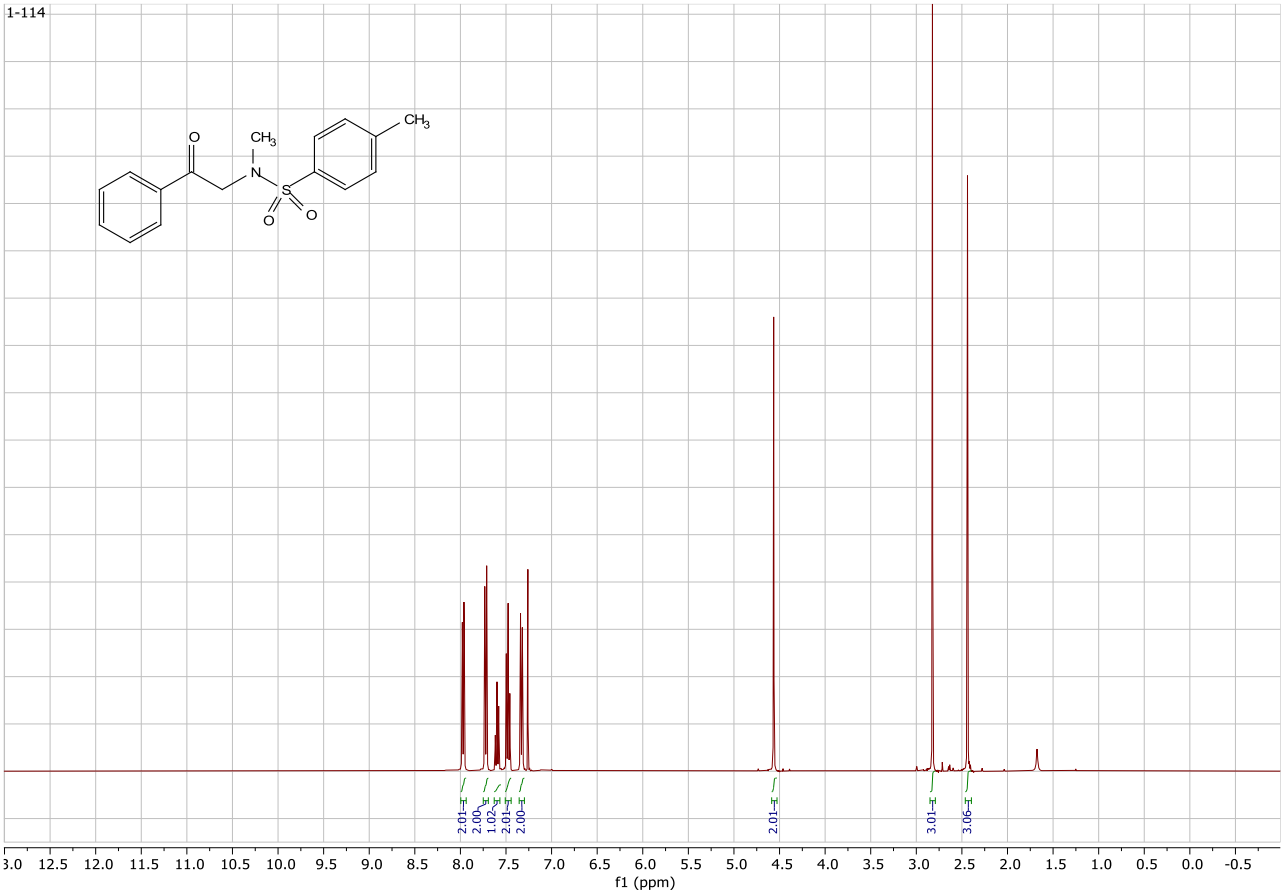
Table of Schrodinger Maestro calculated data:

	Potential Energy[1]	Dihedral angle[1,2] (°)	Atomic Distance[1,3] (Å)	Conversion/Yield (%)
o-H	76.4	11.2	2.53	90/76
o-OMe	19.6	-8.0	2.45	100/82
o-Cl	77.7	91.4	3.09	100/61
o-Br	76.9	-65.7	2.70	100/40
o-Me	68.2	39.1	3.77	50/30

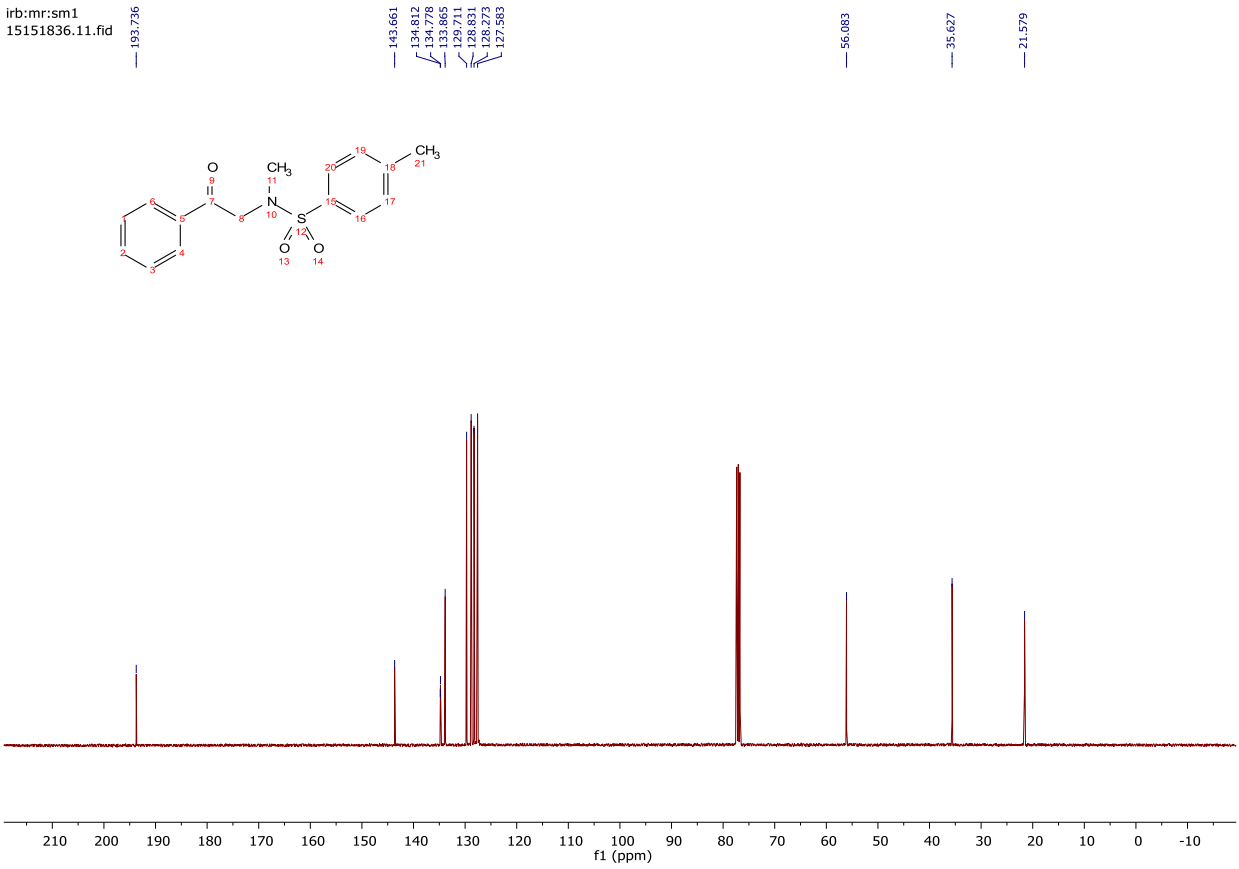
[1]Calculated from the minimized structure in Schrodinger Maestro software using the OPLS3e force field in water with no constraints [2]Dihedral angle between carbonyl and aryl ring [3]Distance from ketone oxygen to closest hydrogen on the *N*-methyl that needs to be abstracted during the reaction

Starting material experimental spectra

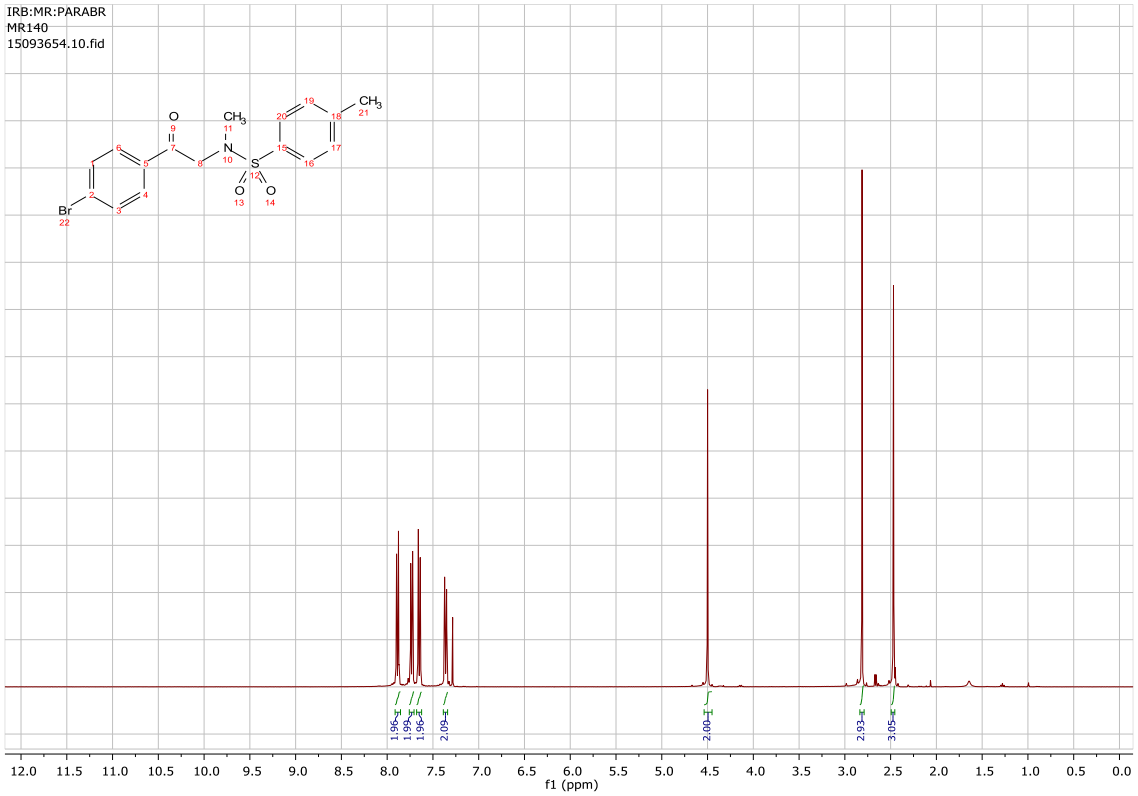
Compound 1-114 ^{1}H NMR (400 MHz, $CDCl_3$)



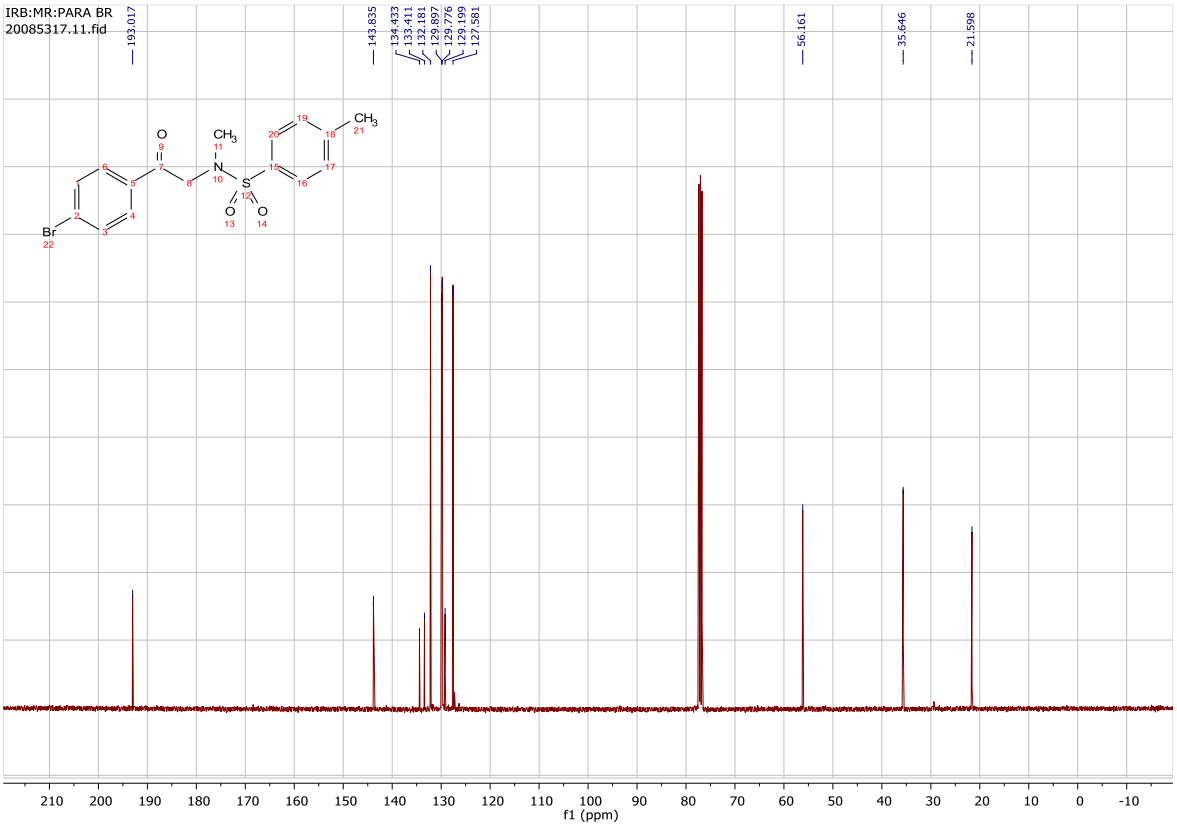
Compound 1-114 ^{13}C{1H} NMR (101 MHz, $CDCl_3$)



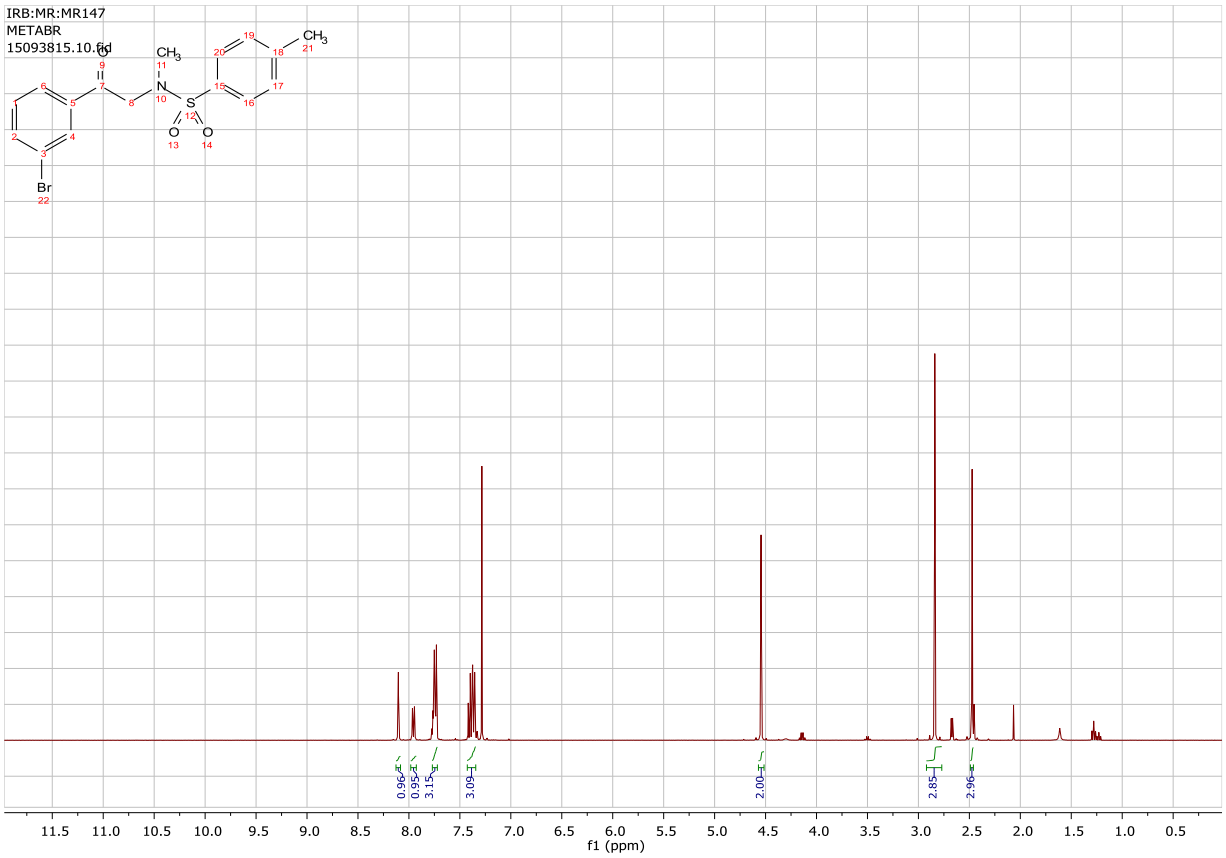
Compound 1-118a ^{1}H NMR (101 MHz, $CDCl_3$)



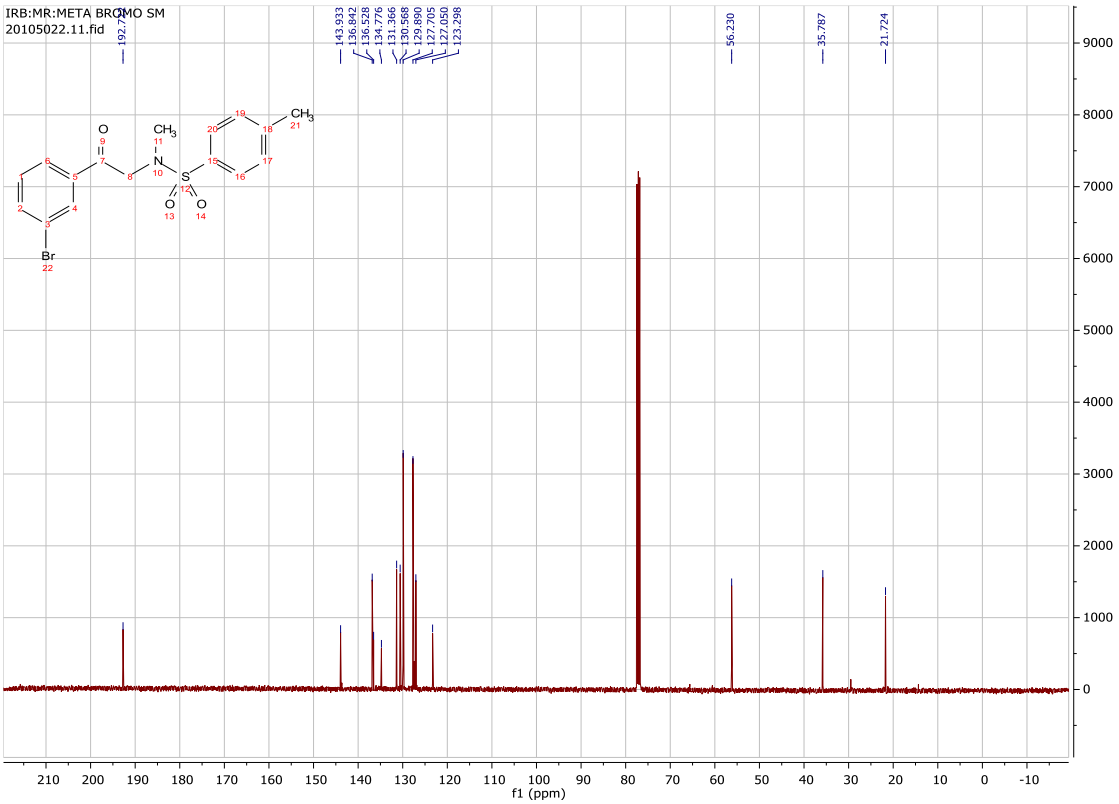
Compound 1-118a ^{13}C{1H} NMR (101 MHz, $CDCl_3$)



Compound 1-119a ^{1}H NMR (101 MHz, $CDCl_3$)



Compound 1-119a ^{13}C{1H} NMR (101 MHz, $CDCl_3$)



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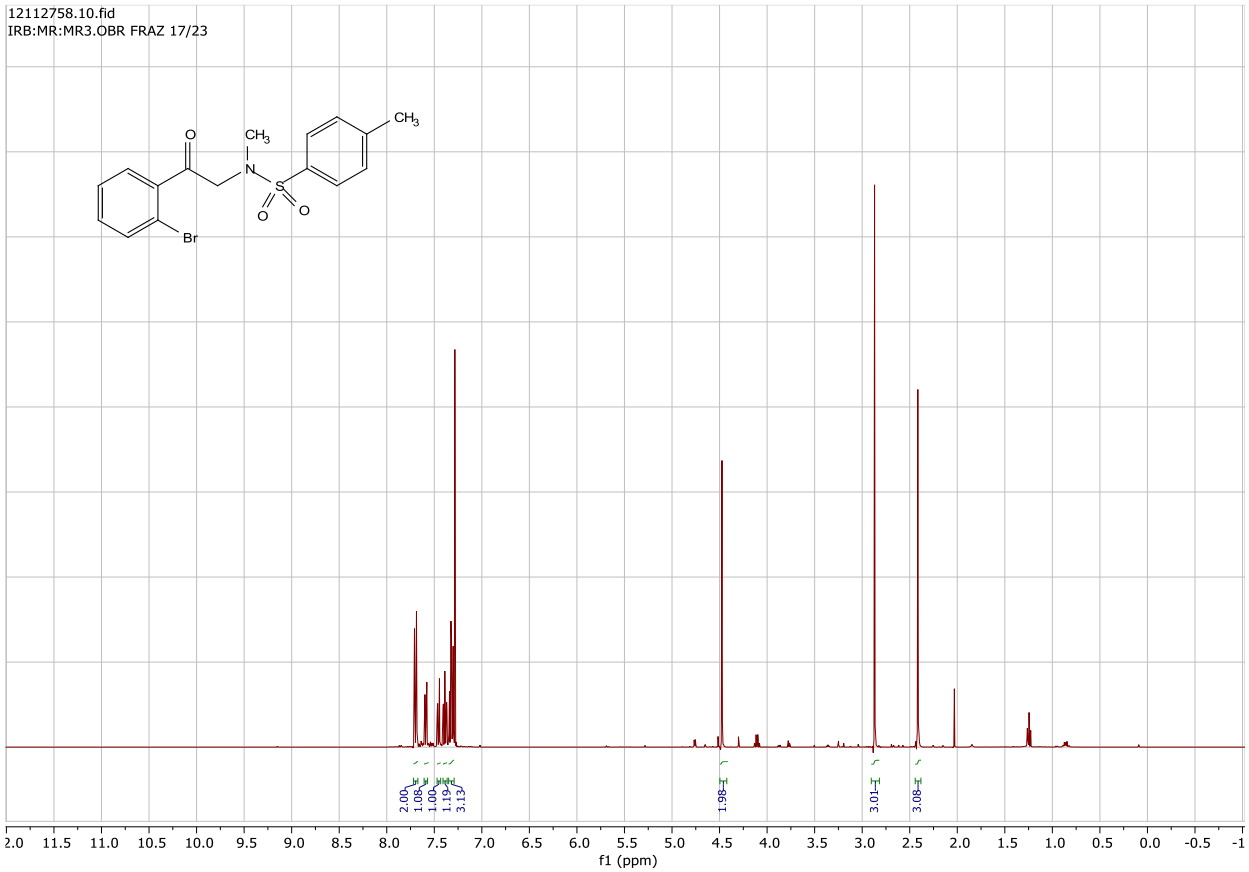
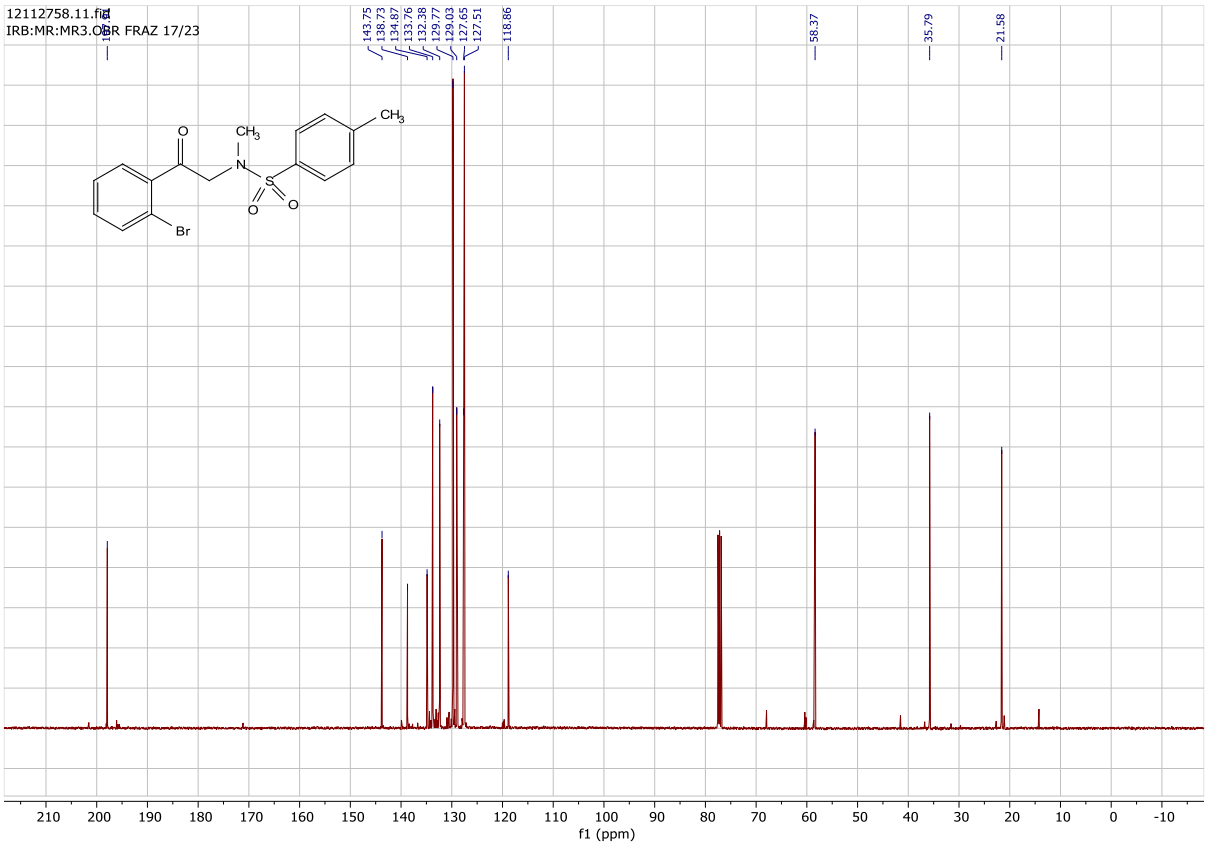
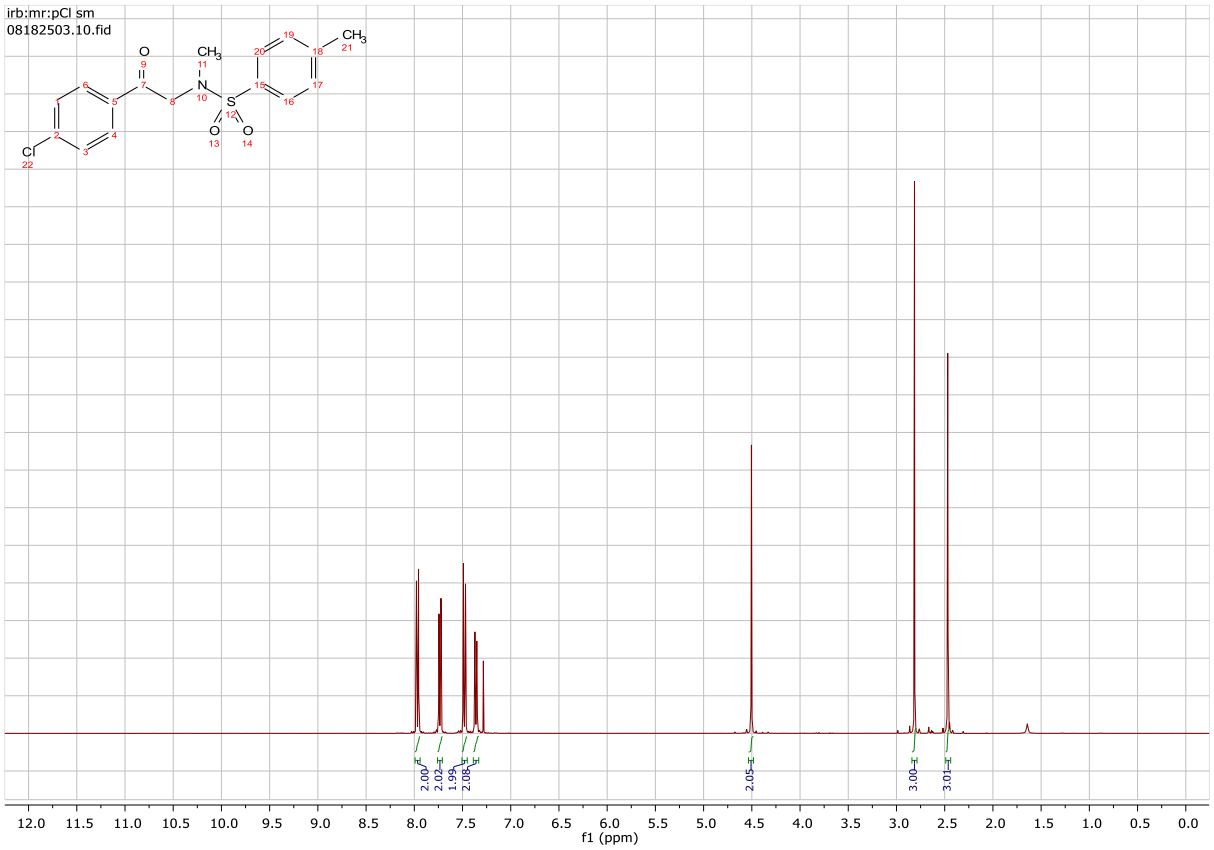


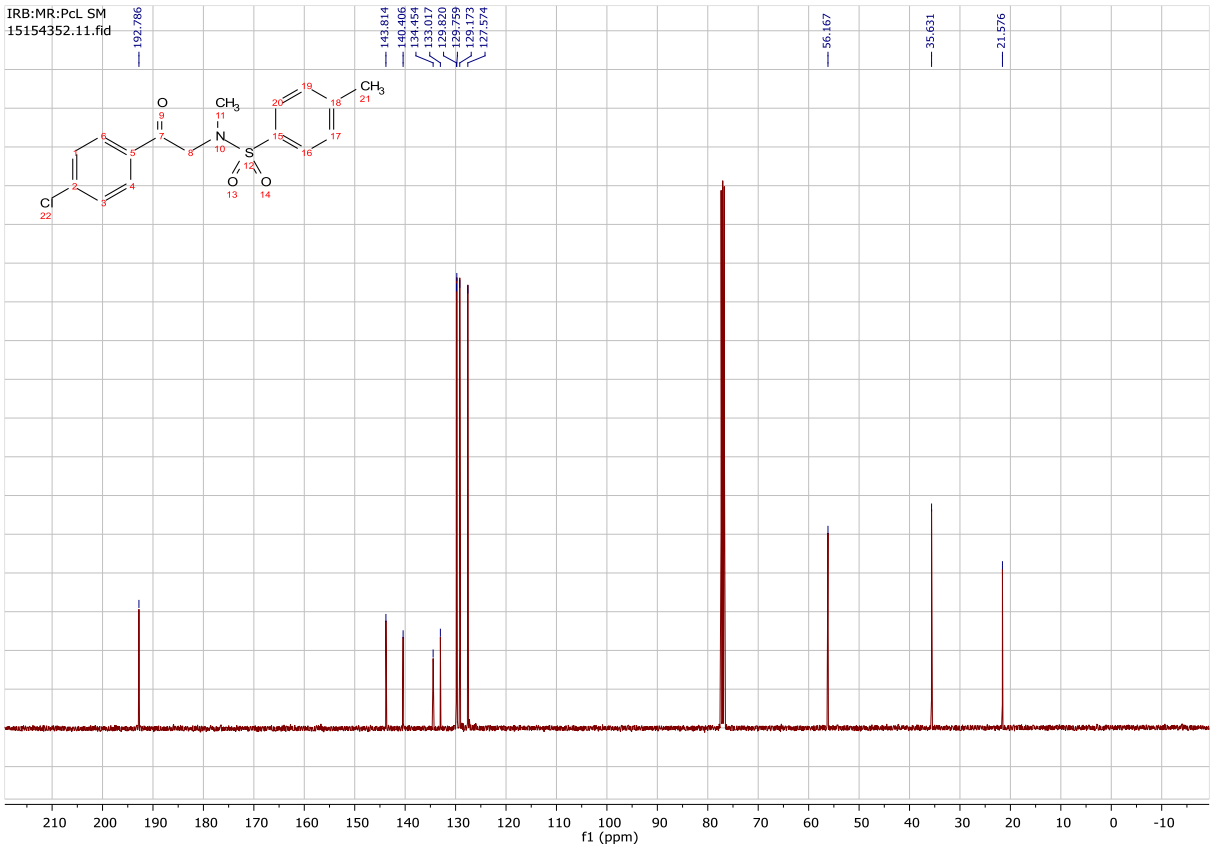
Compound 1-120a ^{13}C{1H} NMR (101 MHz, $CDCl_3$)



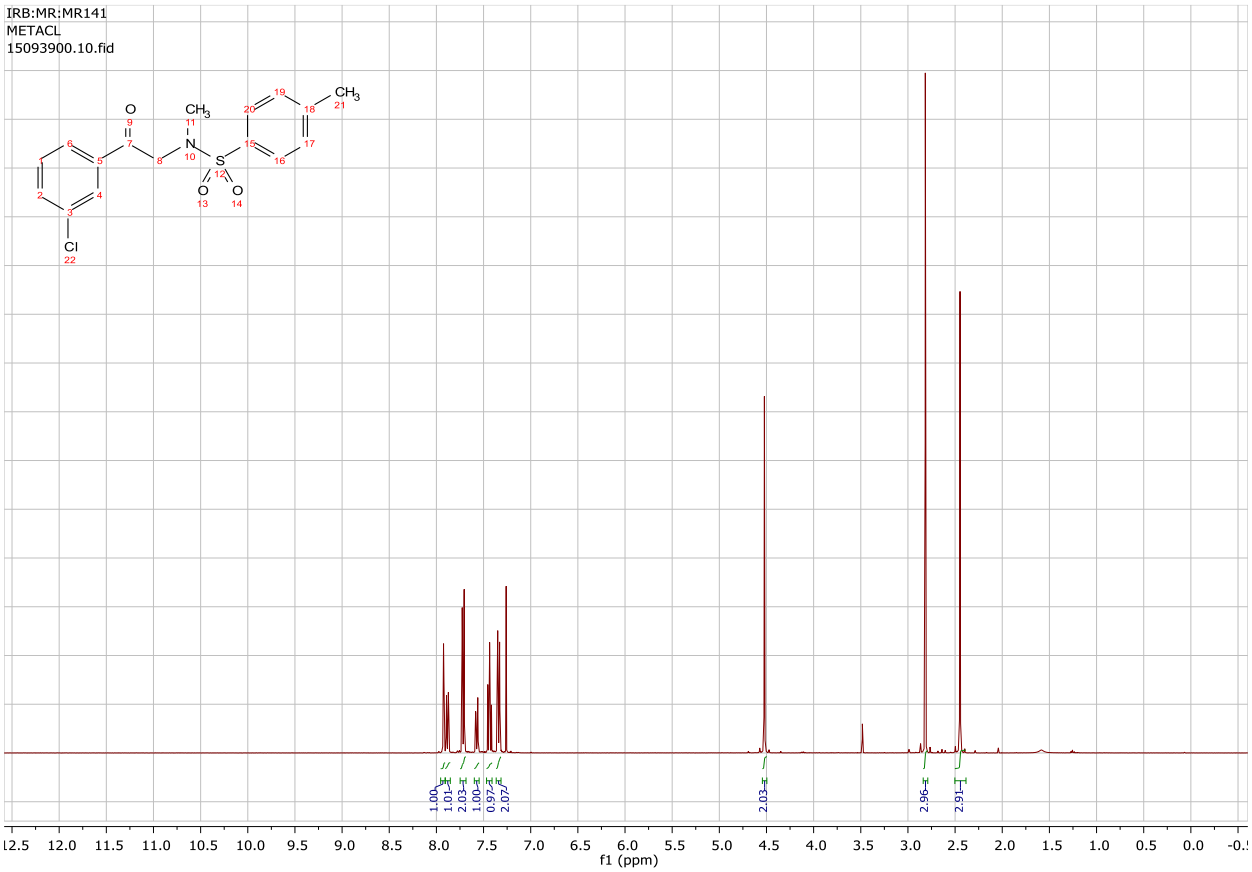
Compound 1-121a ^{1}H NMR (101 MHz, $CDCl_3$)



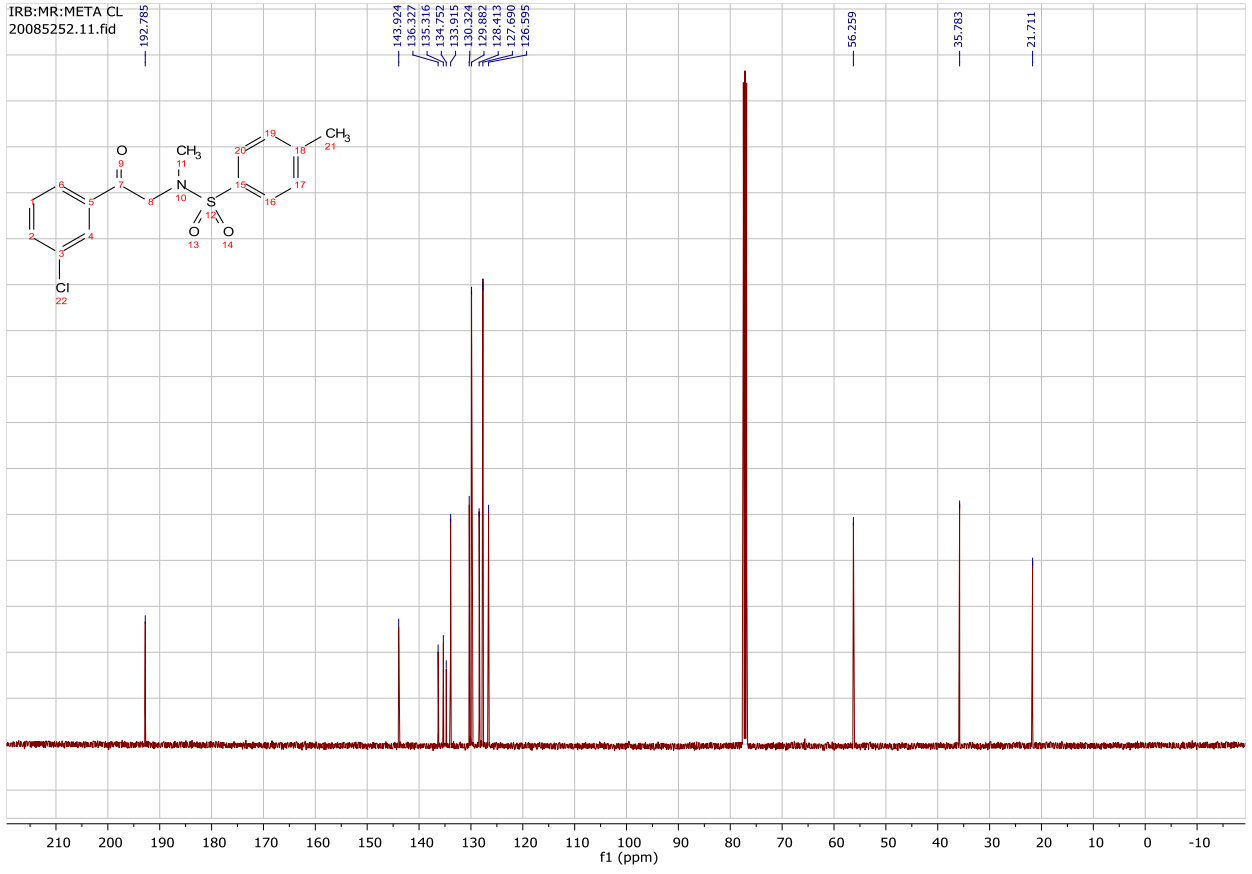
Compound 1-121a ^{13}C{1H} NMR (101 MHz, $CDCl_3$)



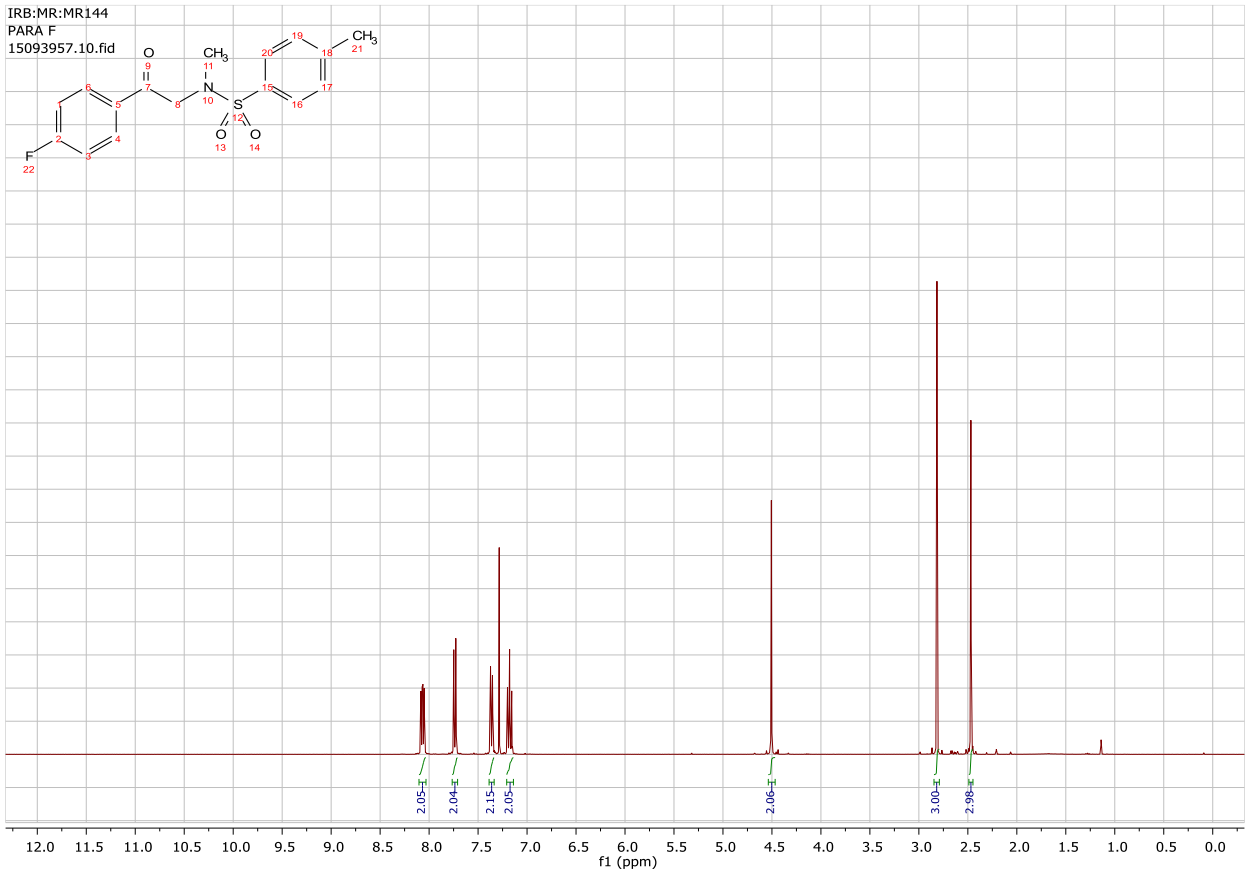
Compound 1-122a ^{1}H NMR (101 MHz, $CDCl_3$)



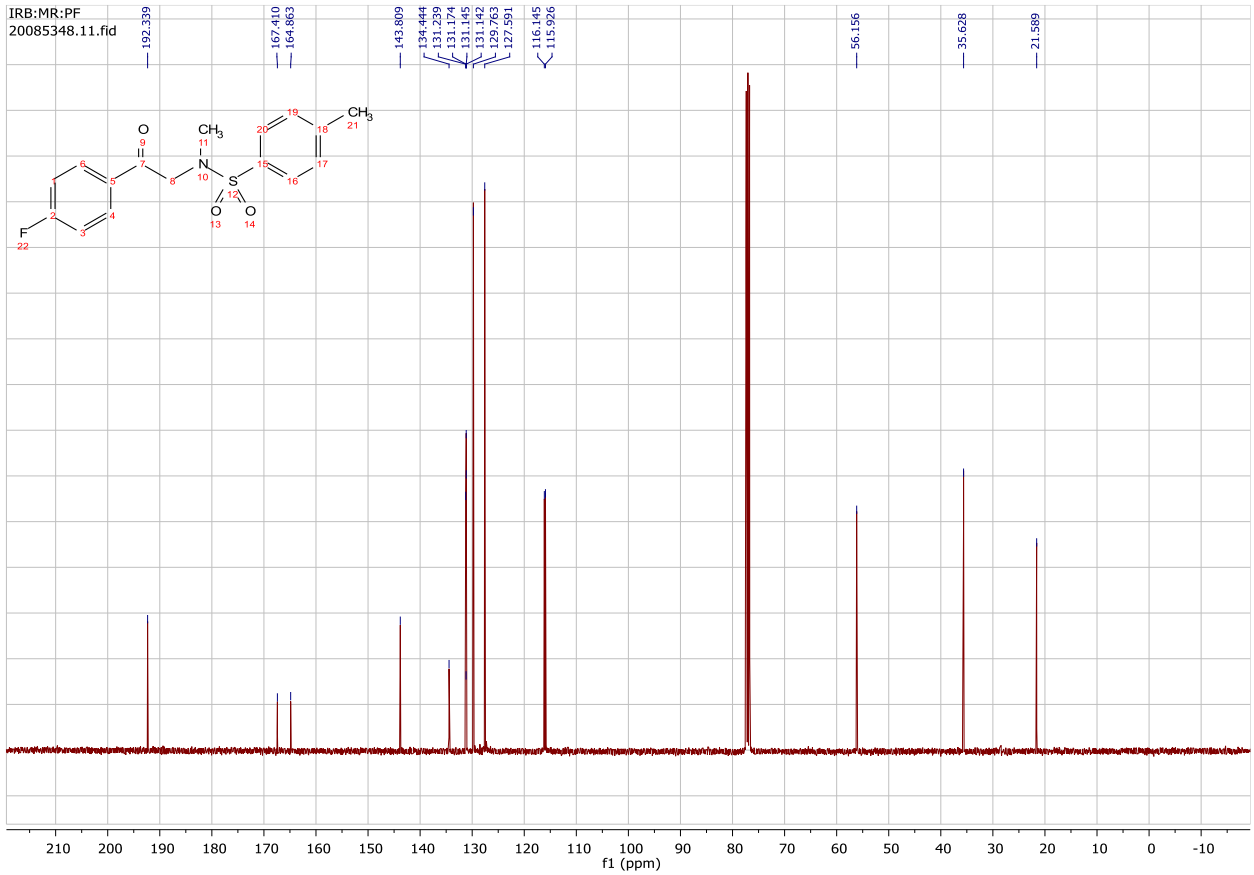
Compound 1-122a ^{13}C{1H} NMR (101 MHz, $CDCl_3$)



Compound 1-124a ^{1}H NMR (101 MHz, $CDCl_3$)



Compound 1-124a ^{13}C{1H} NMR (101 MHz, $CDCl_3$)



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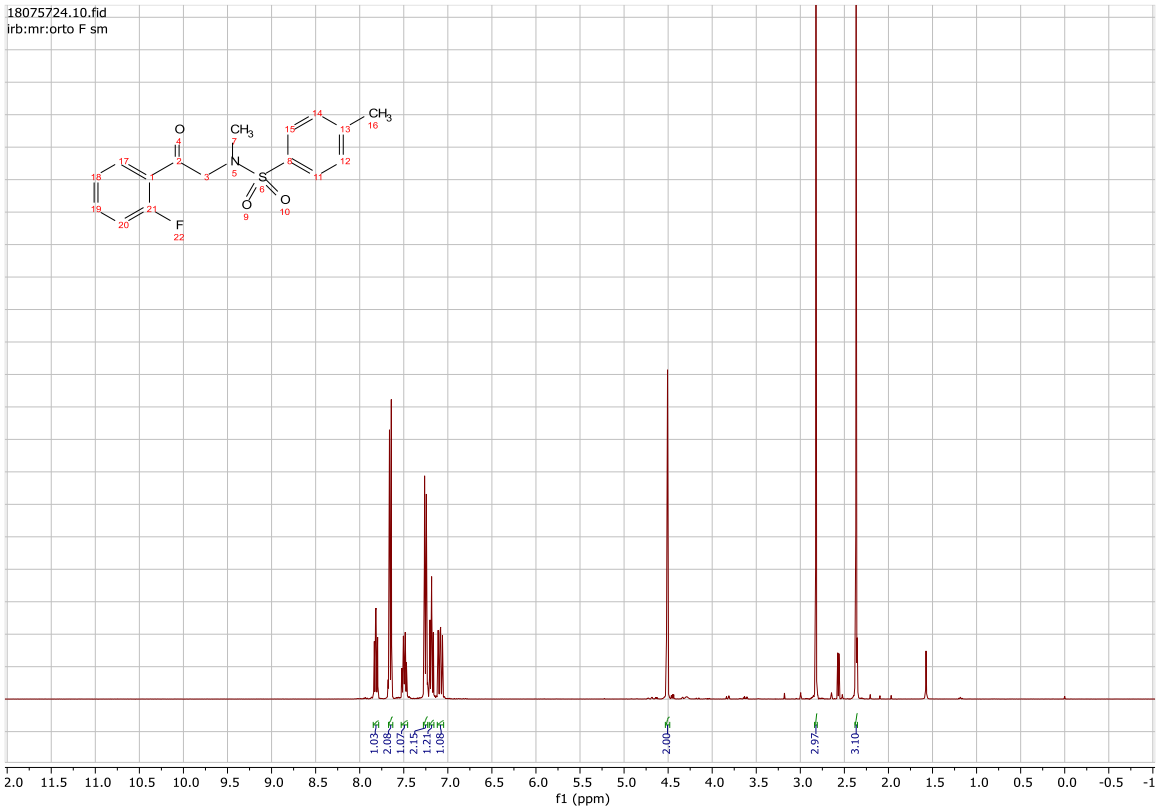

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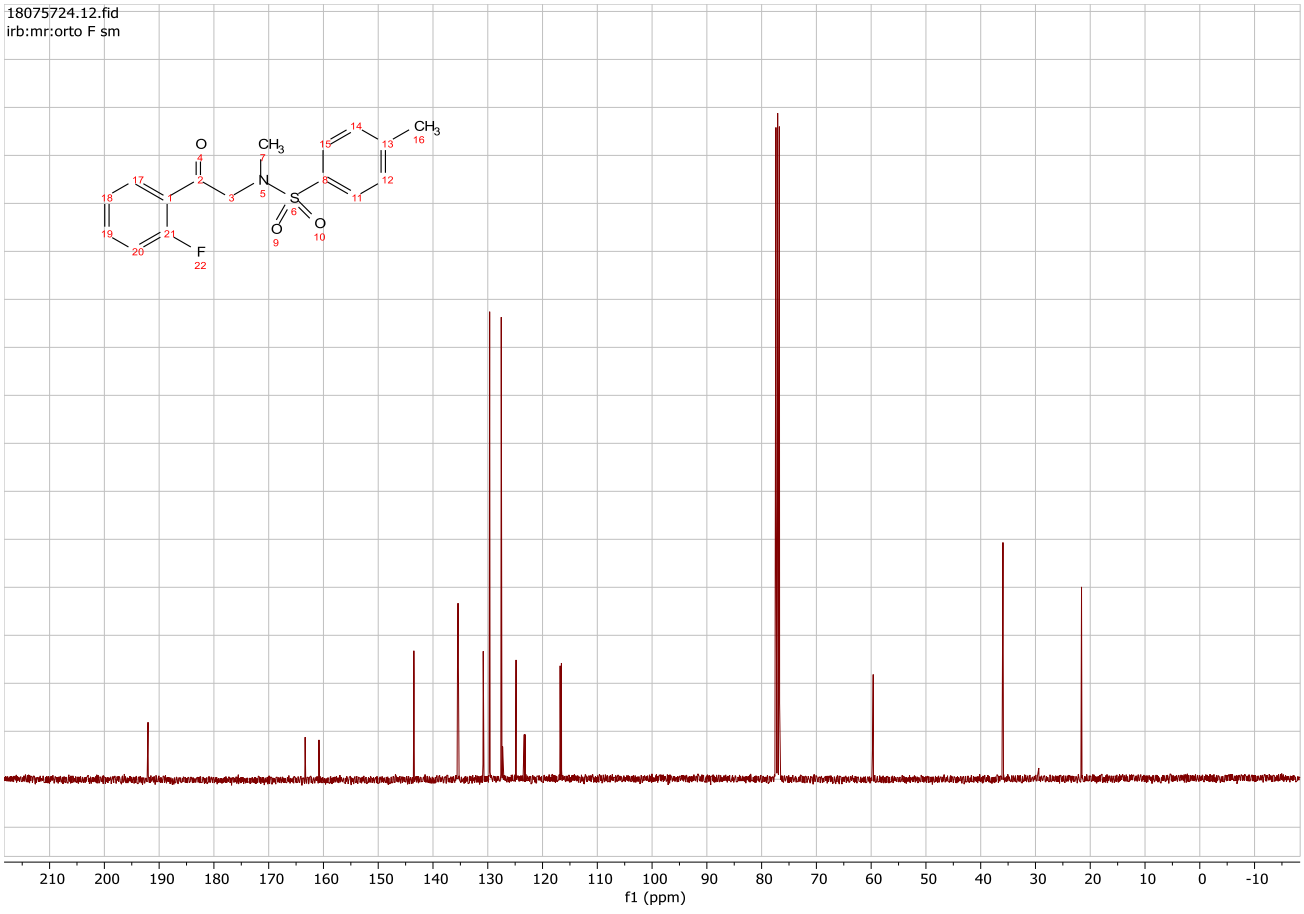

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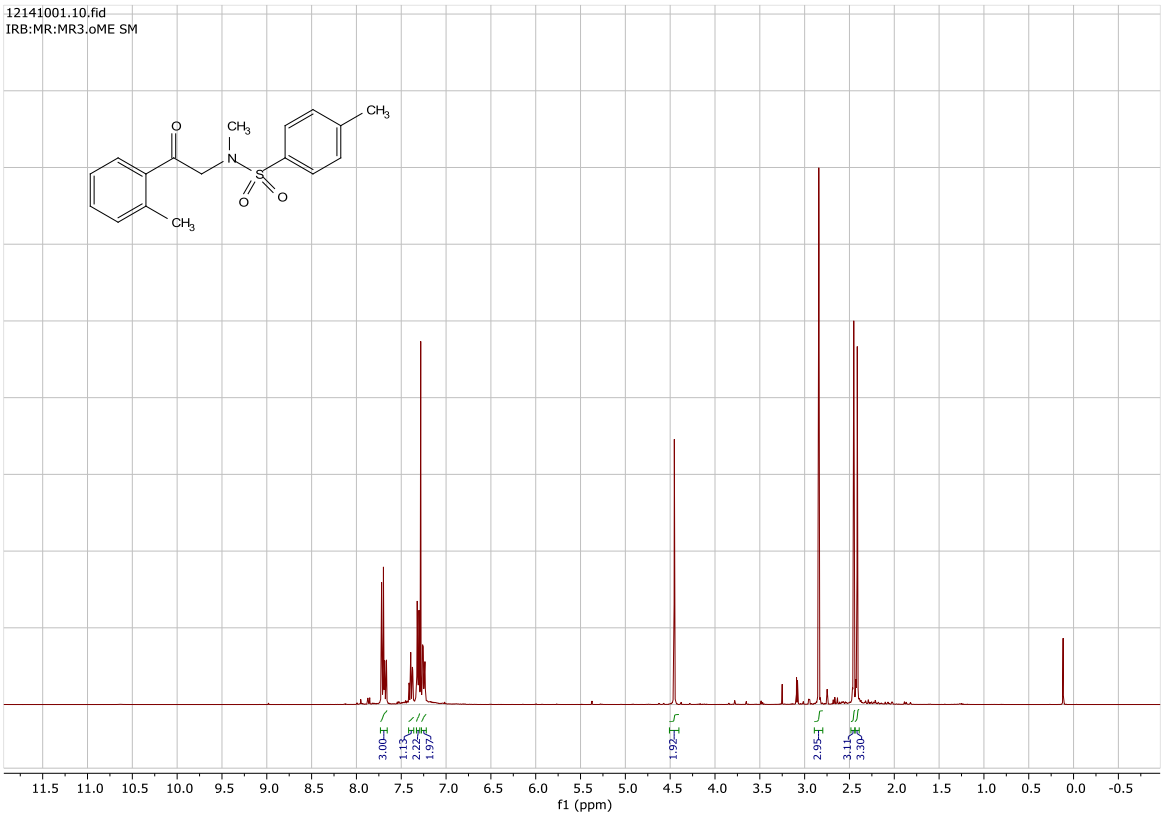
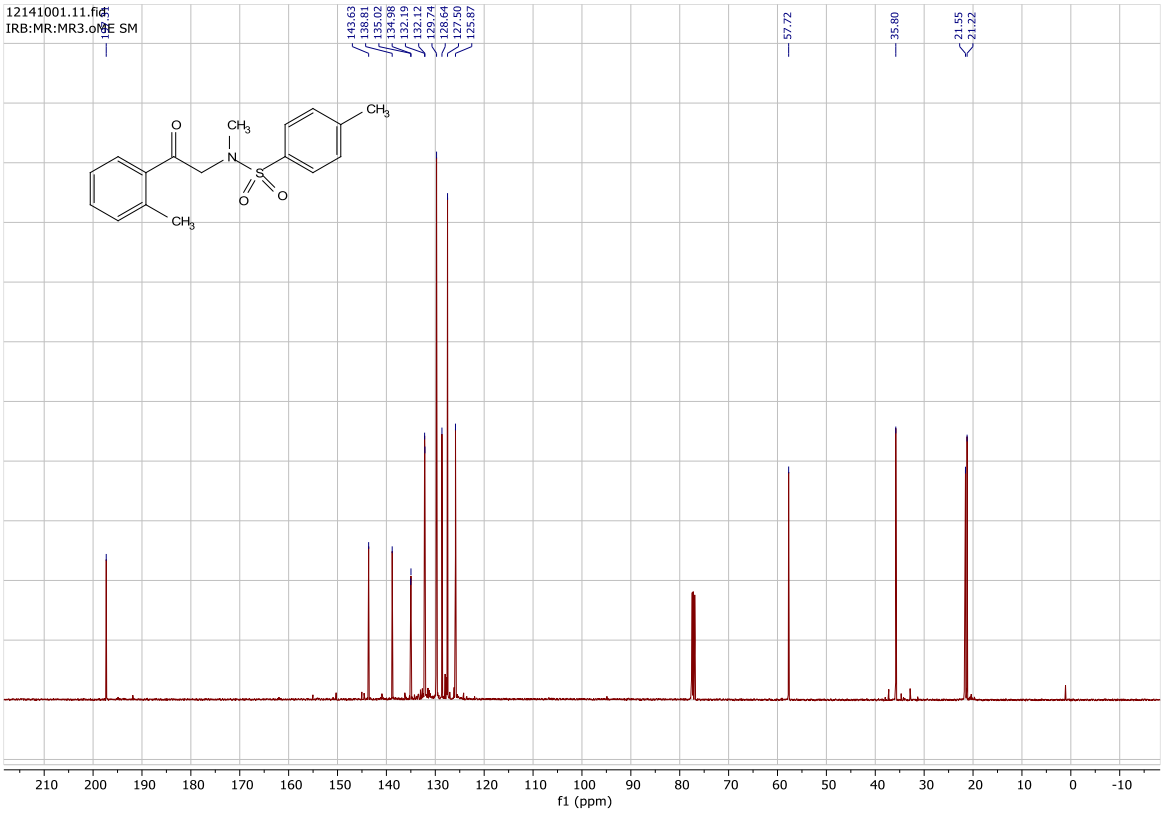


Compound 1-126a ^{13}C{1H} NMR (101 MHz, $CDCl_3$)



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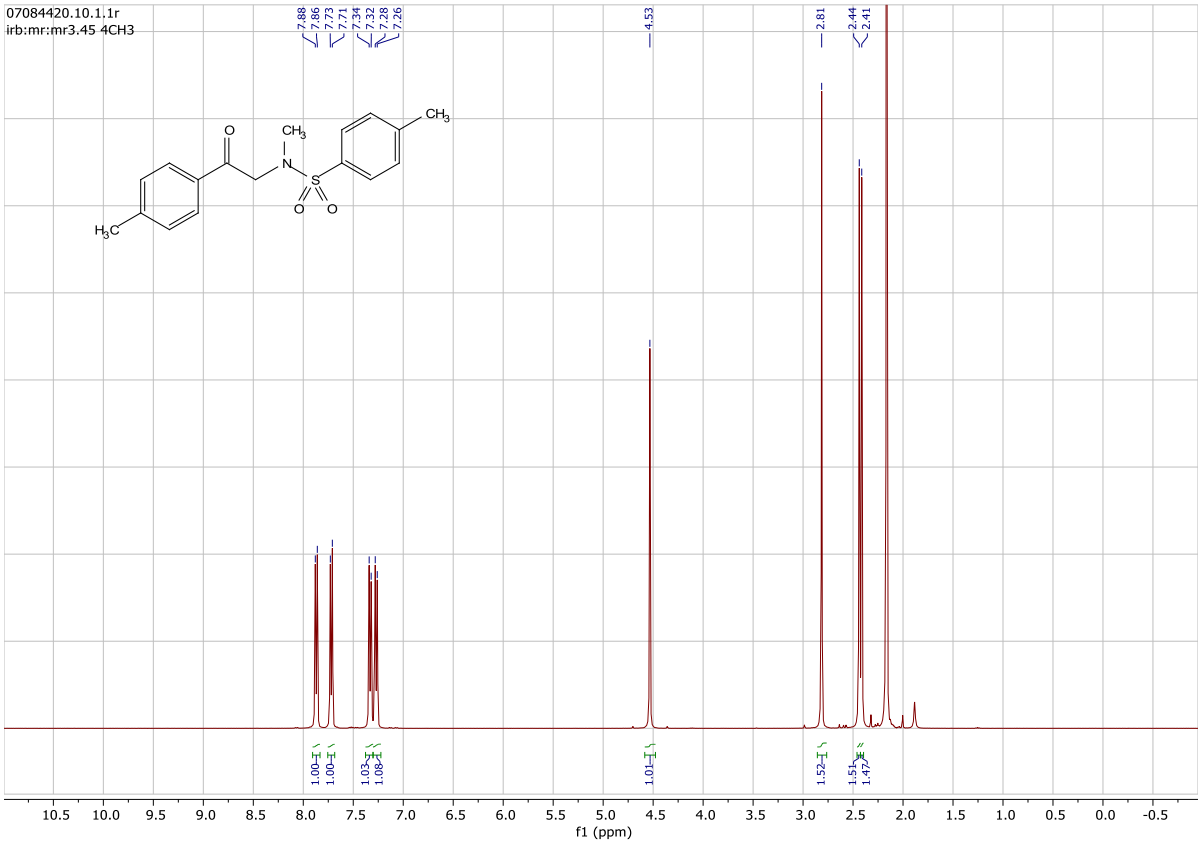
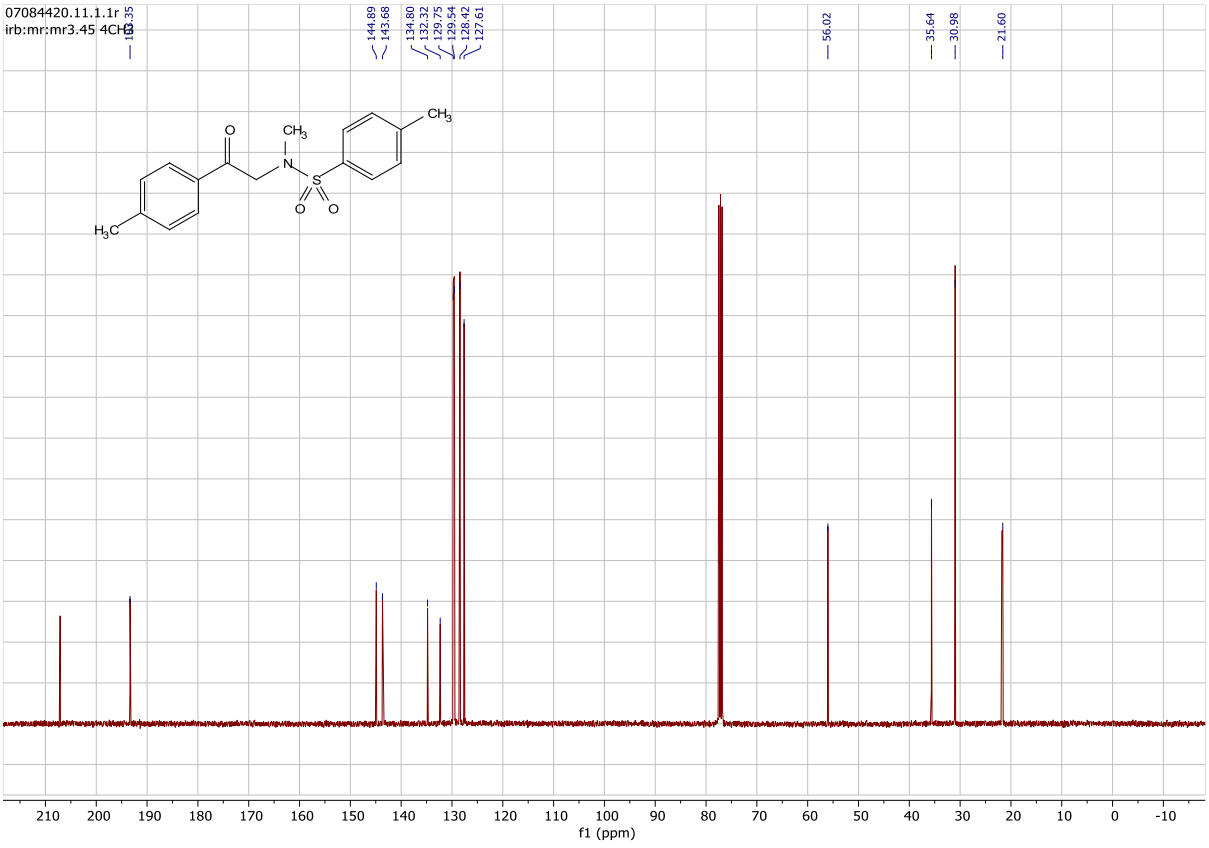
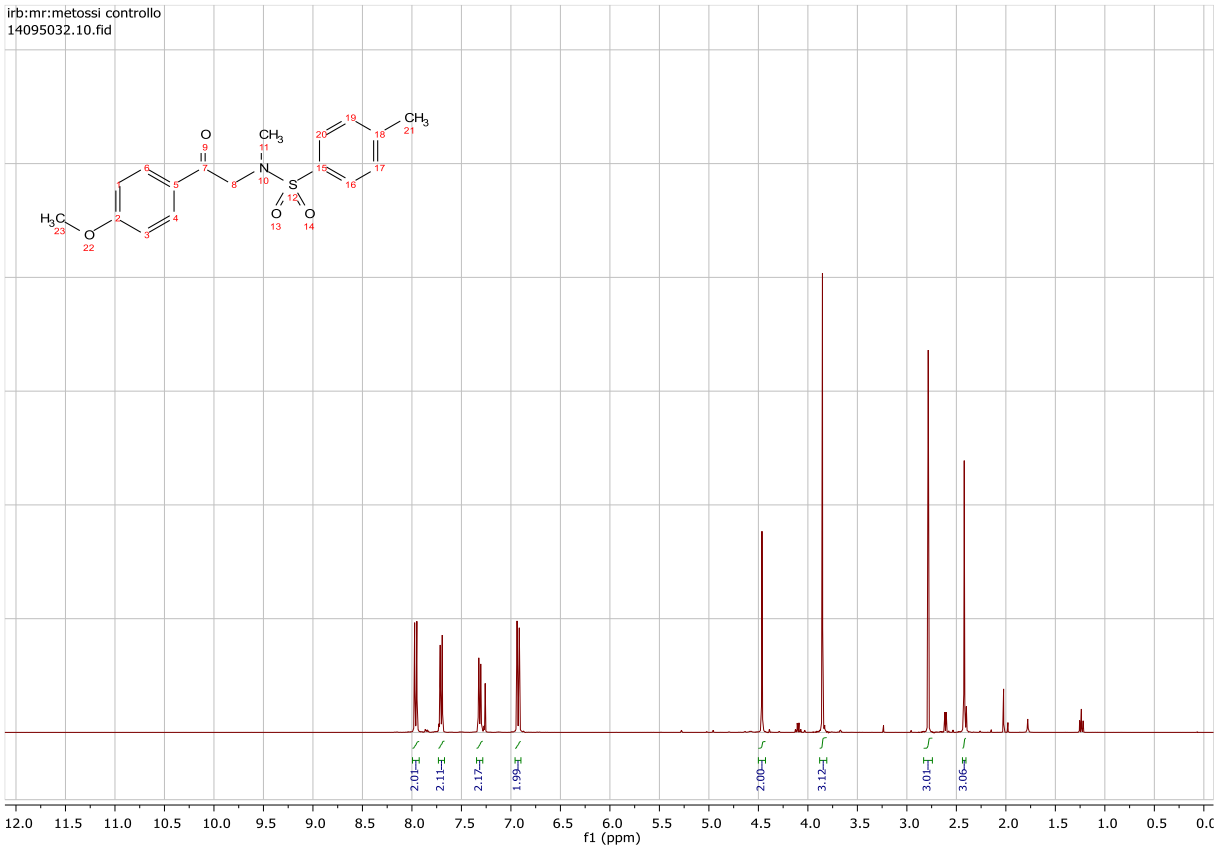


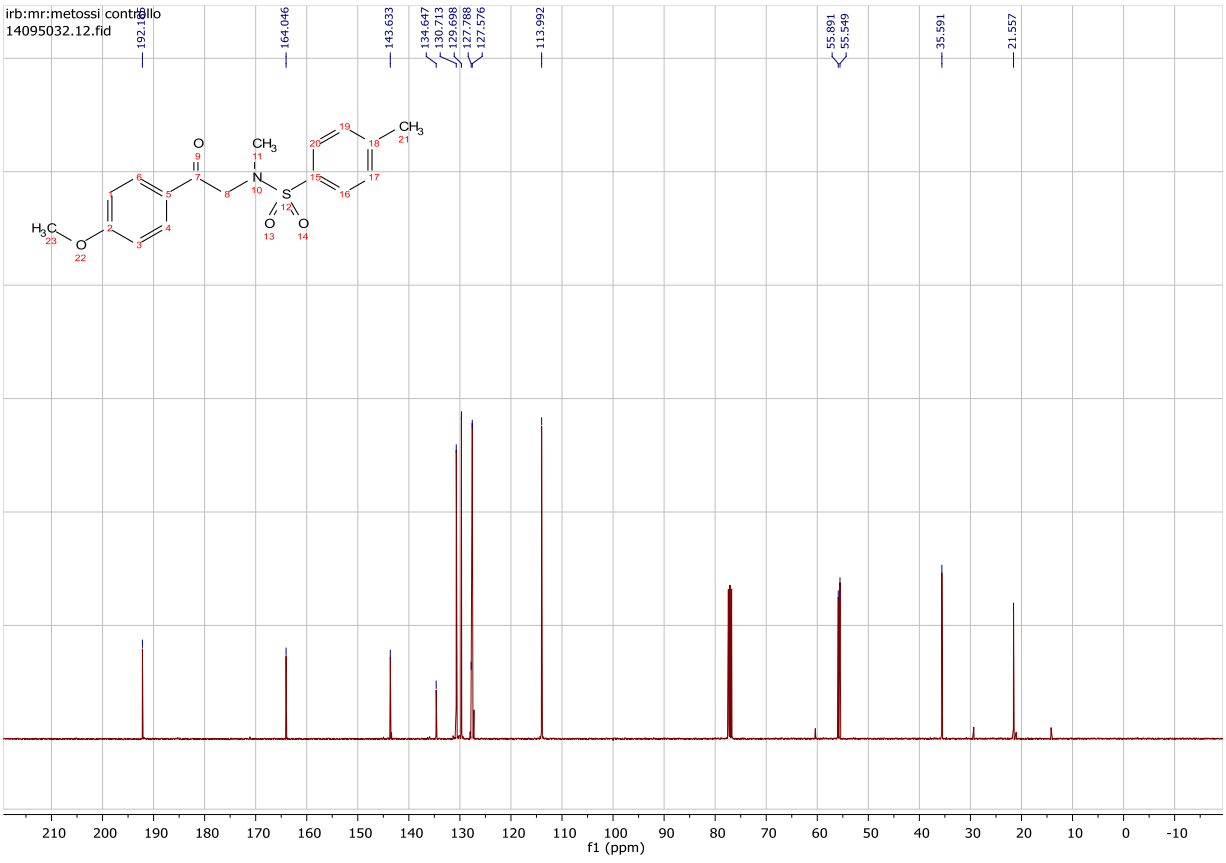
Compound 1-127a ^{13}C{1H} NMR (101 MHz, $CDCl_3$)



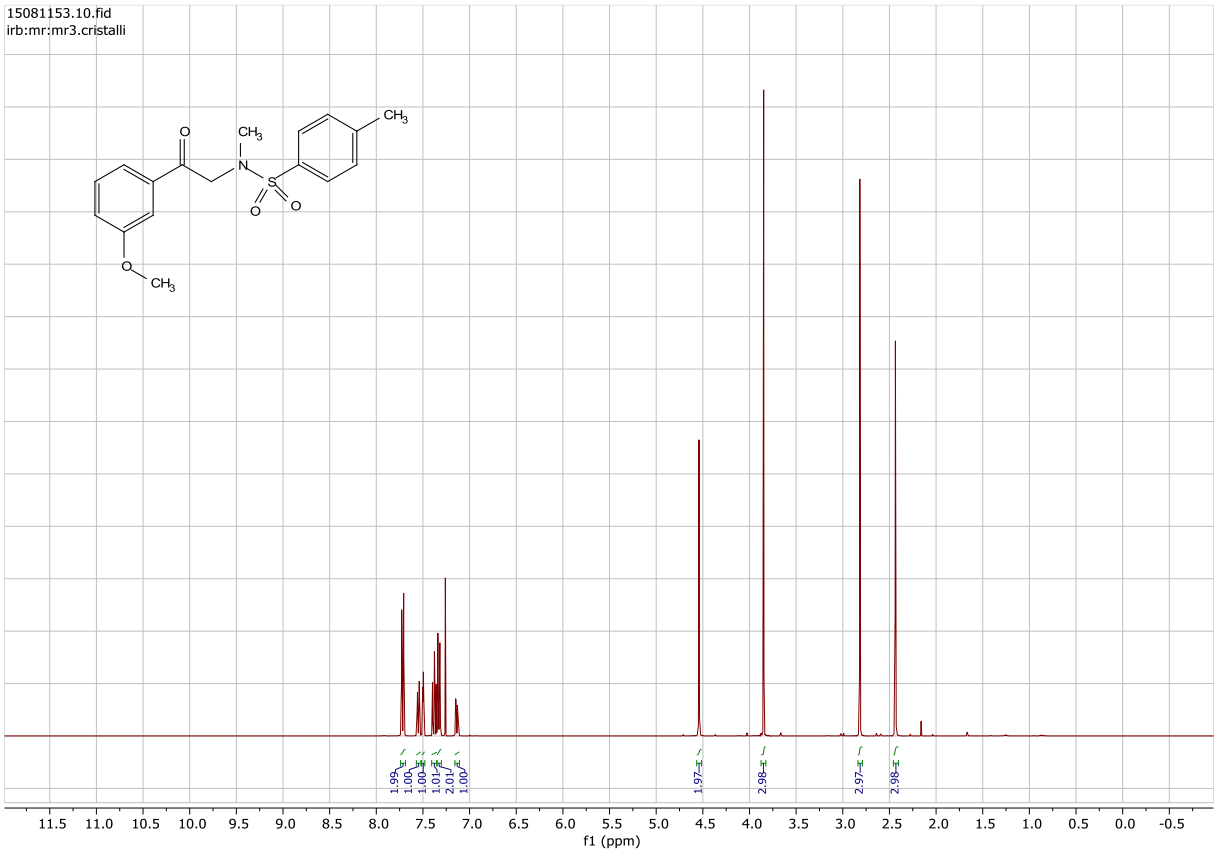
Compound 1-128a ^{1}H NMR (101 MHz, $CDCl_3$)



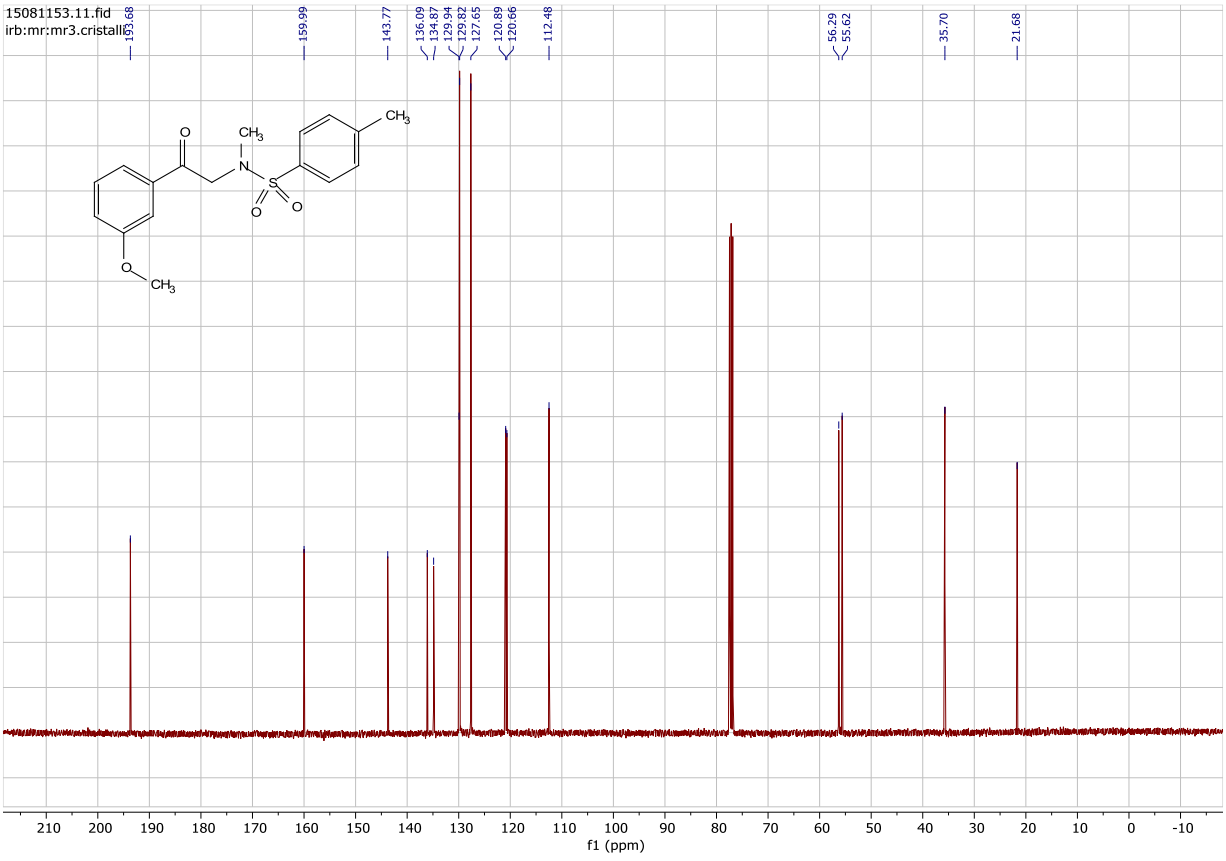
Compound 1-128a ^{13}C{1H} NMR (101 MHz, $CDCl_3$)



Compound 1-129a ^{1}H NMR (101 MHz, $CDCl_3$)



Compound 1-129a $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



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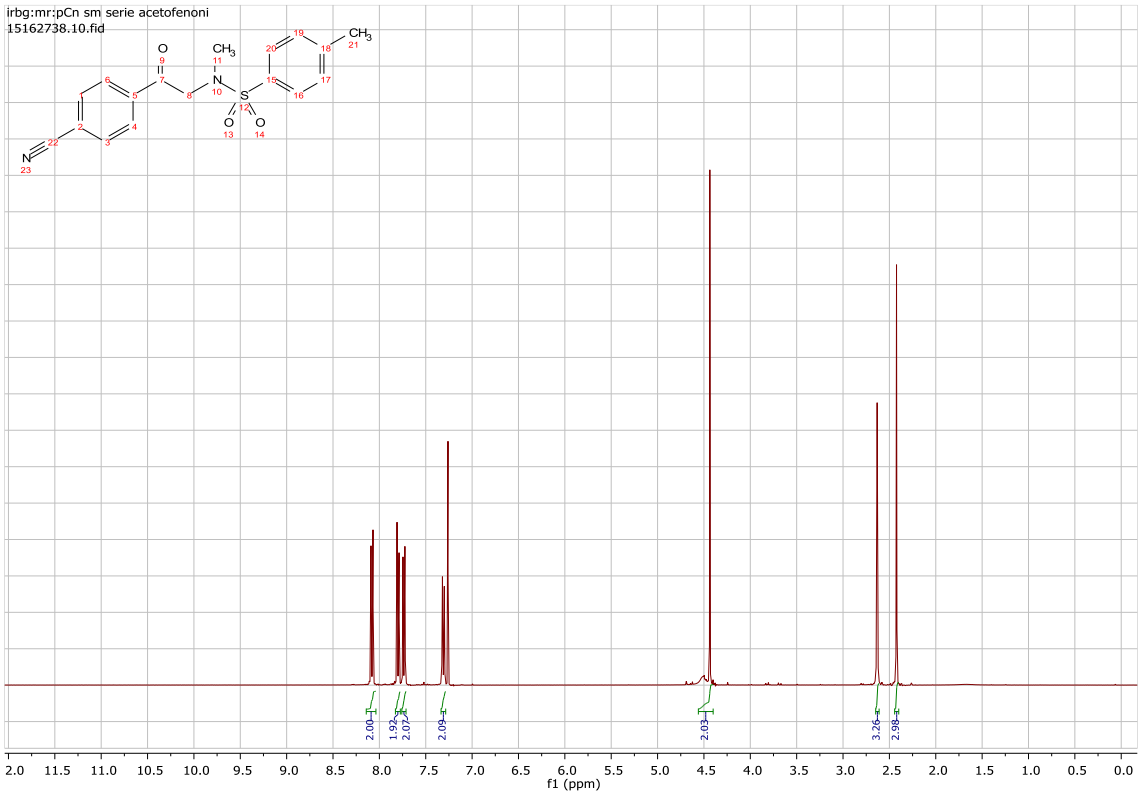

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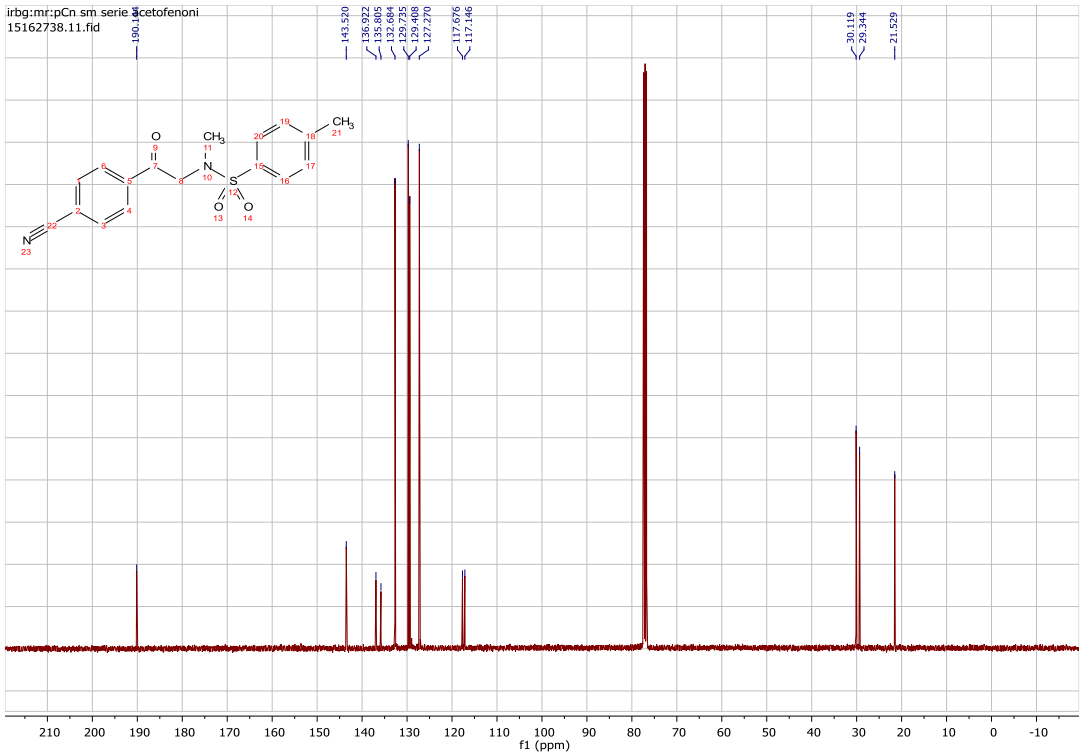

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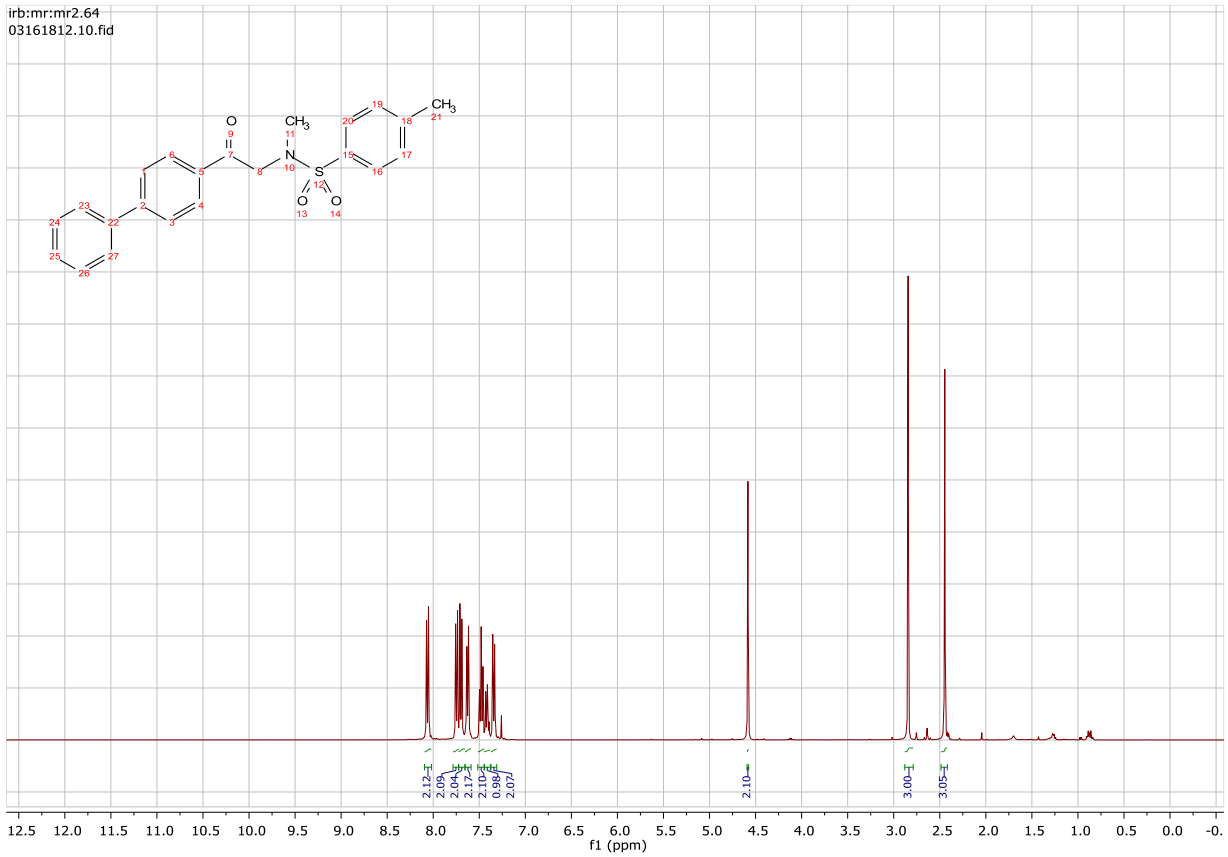

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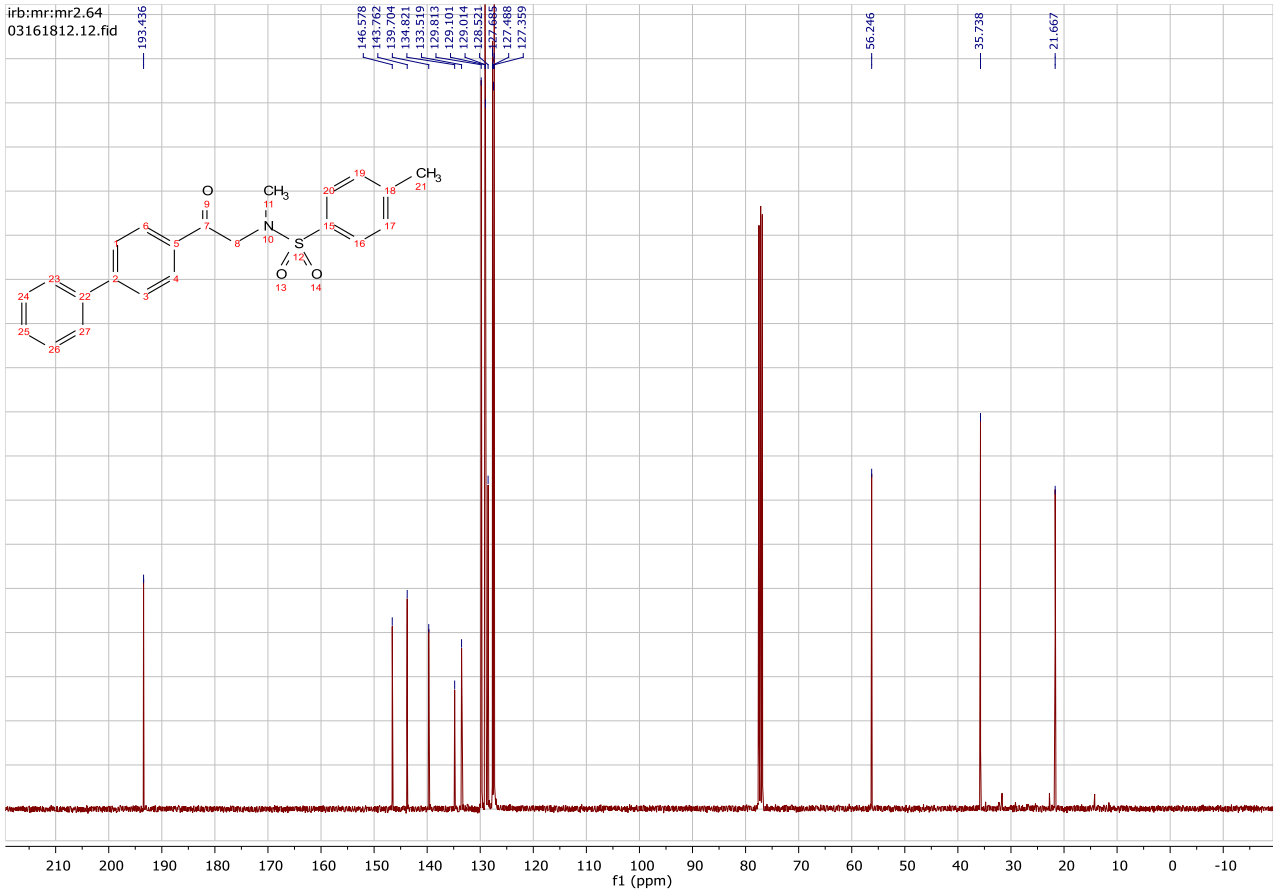
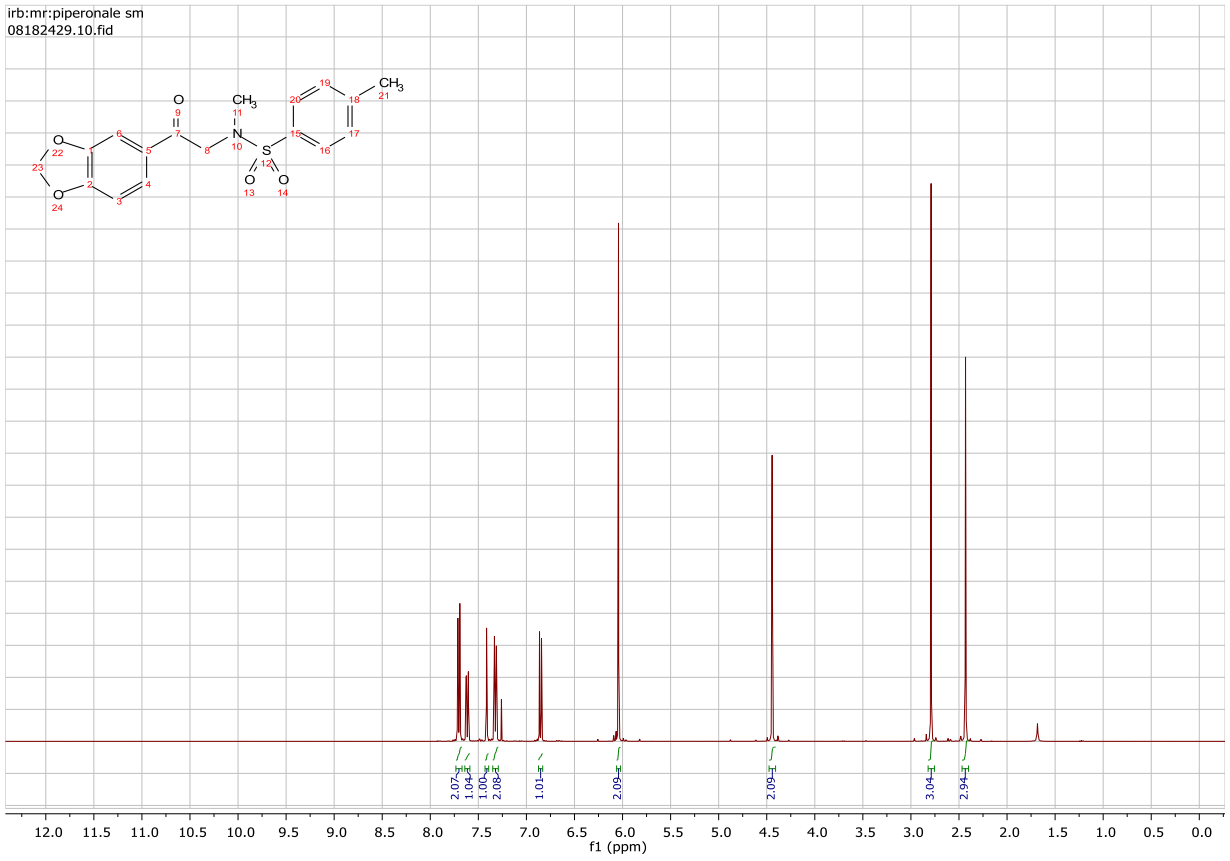
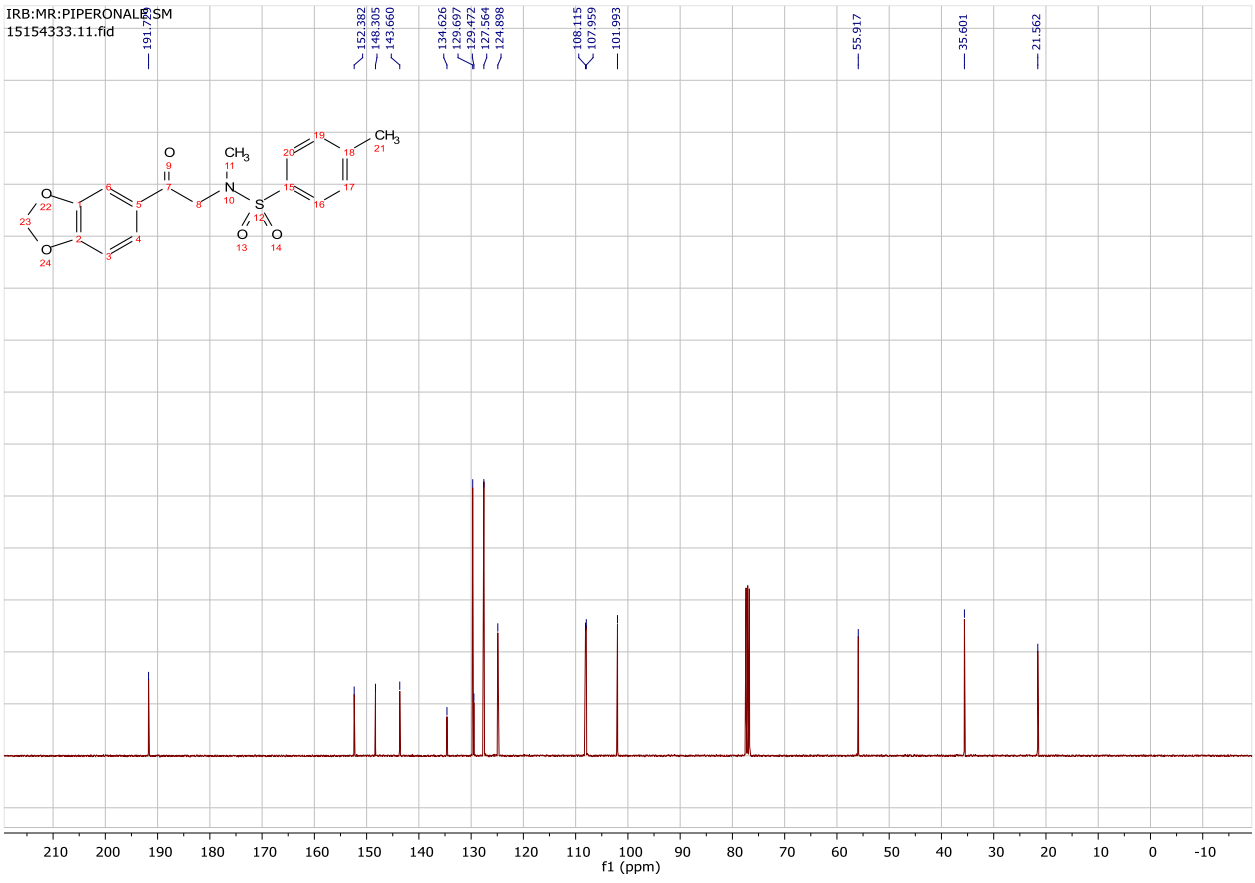


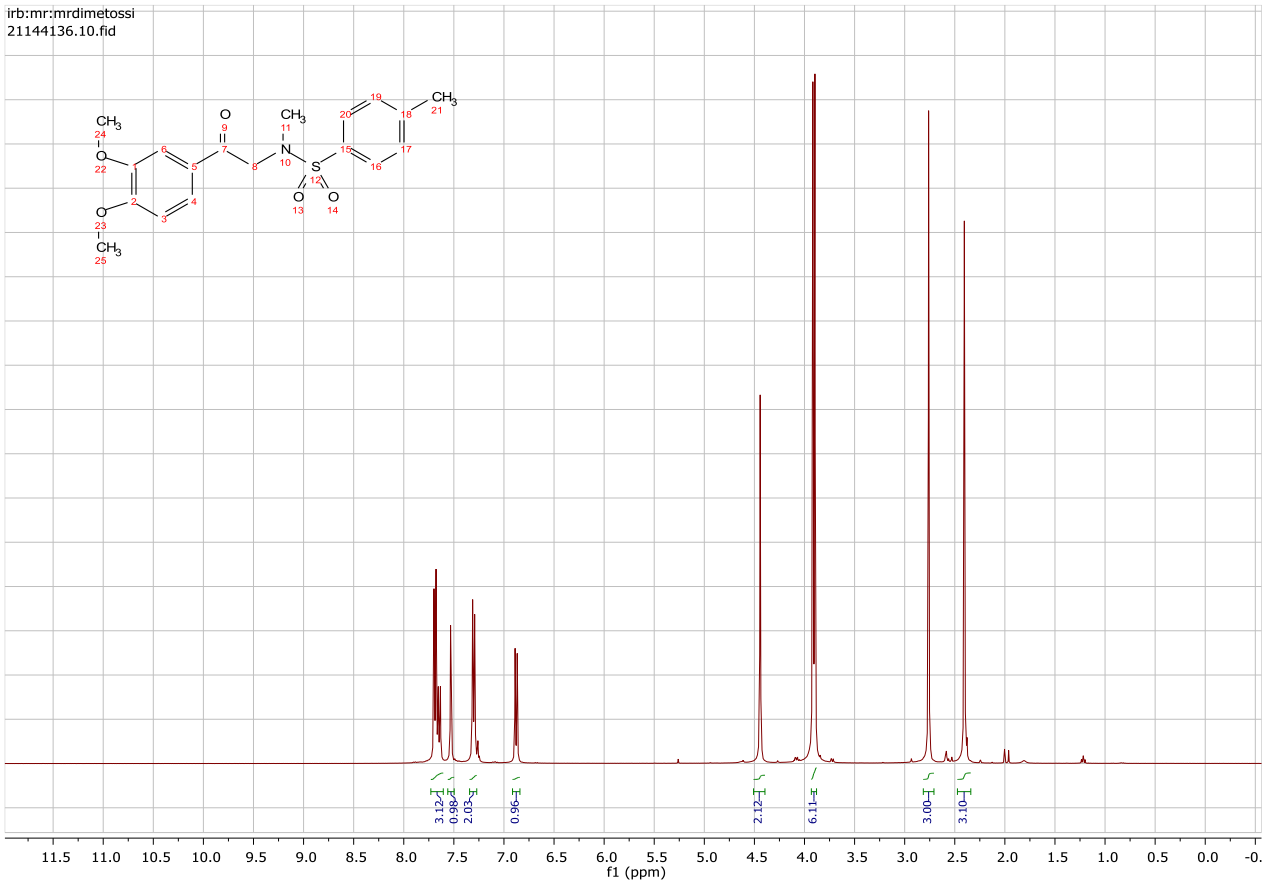
Compound 1-133a ^{1}H NMR (101 MHz, $CDCl_3$)



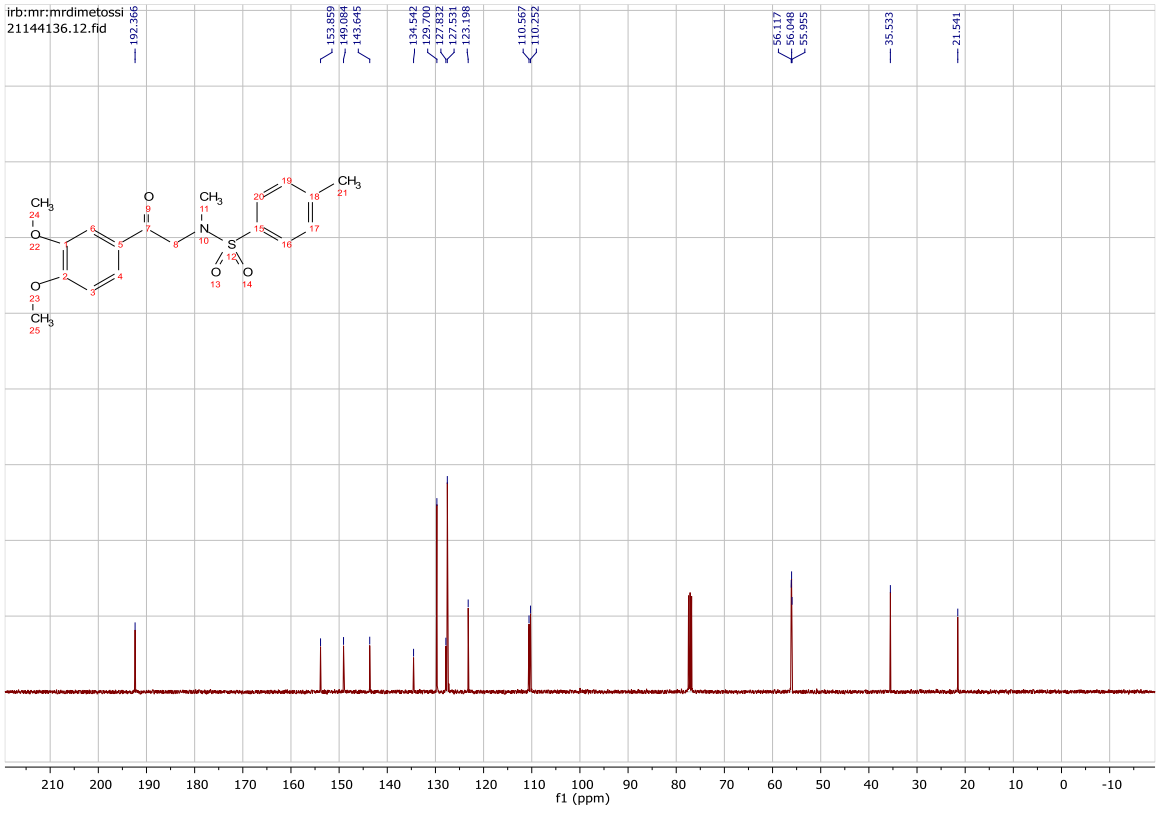
Compound 1-133a ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



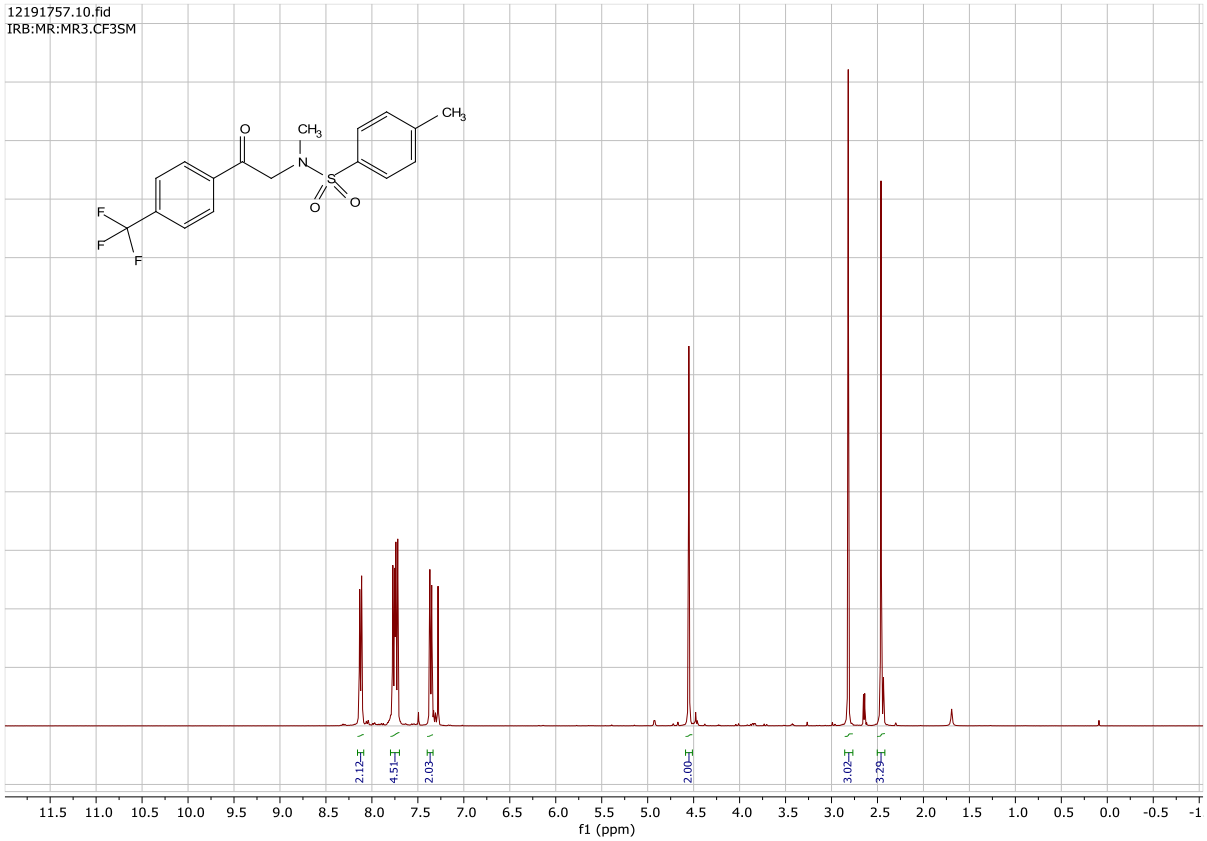
Compound 1-134a ^{1}H NMR (101 MHz, $CDCl_3$)



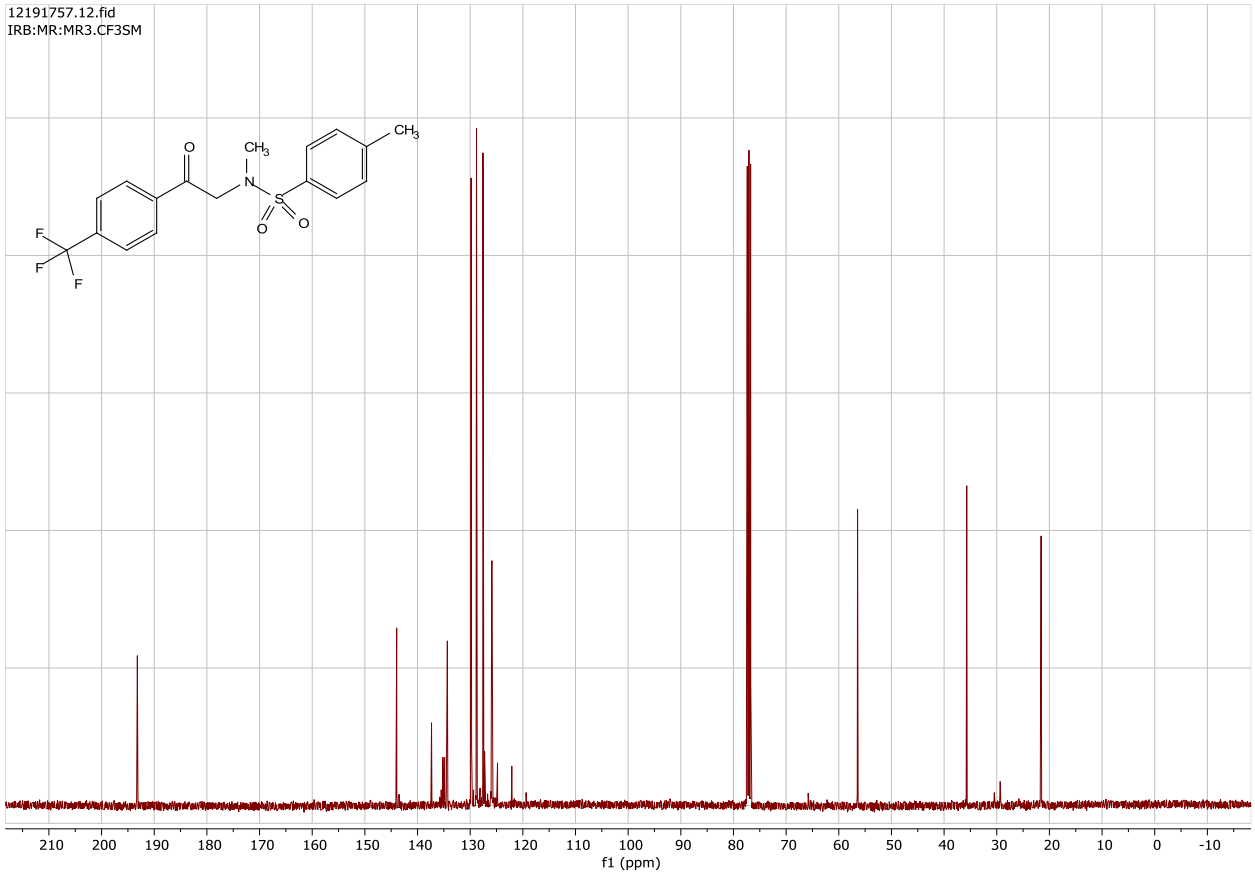
Compound 1-134a ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



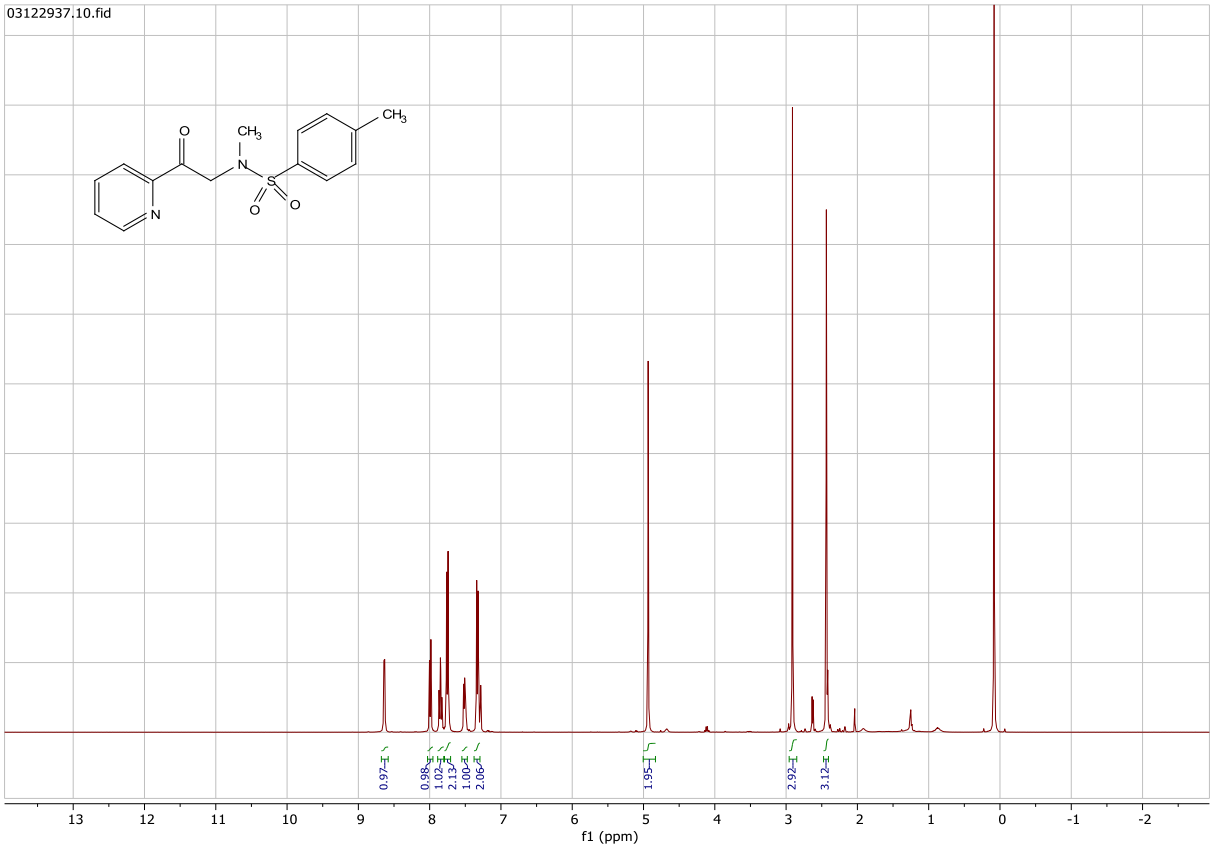
Compound 1-135a ^{1}H NMR (101 MHz, $CDCl_3$)



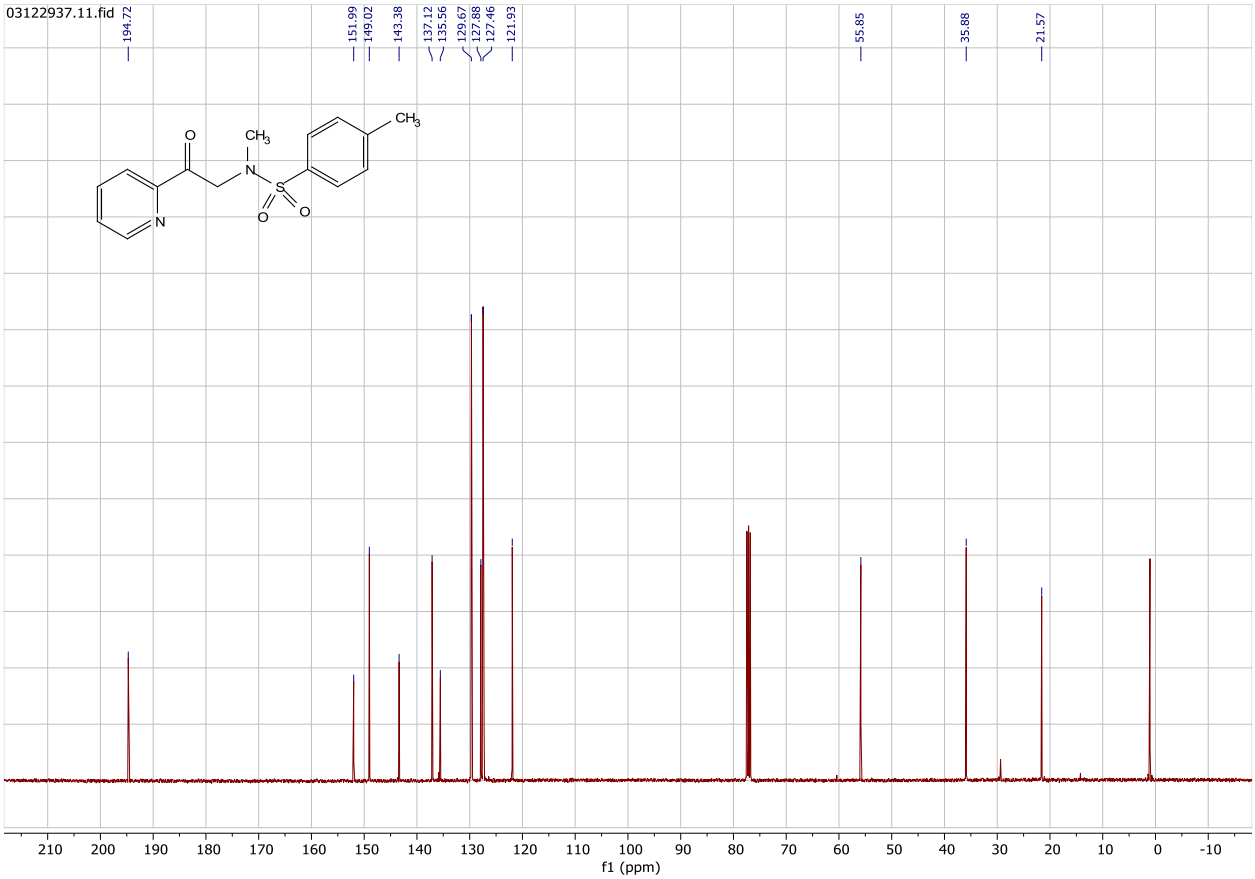
Compound 1-135a ^{13}C{1H} NMR (101 MHz, $CDCl_3$)



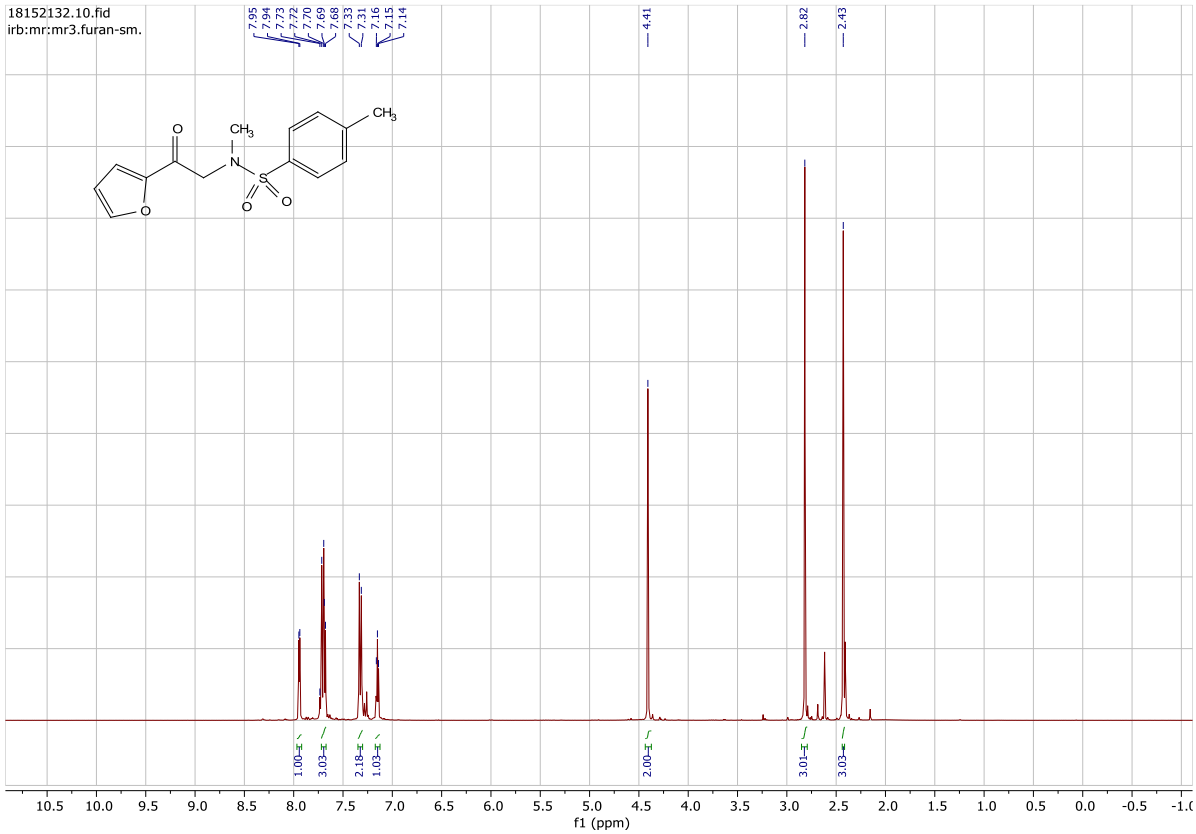
Compound 1-136a ^{1}H NMR (101 MHz, $CDCl_3$)



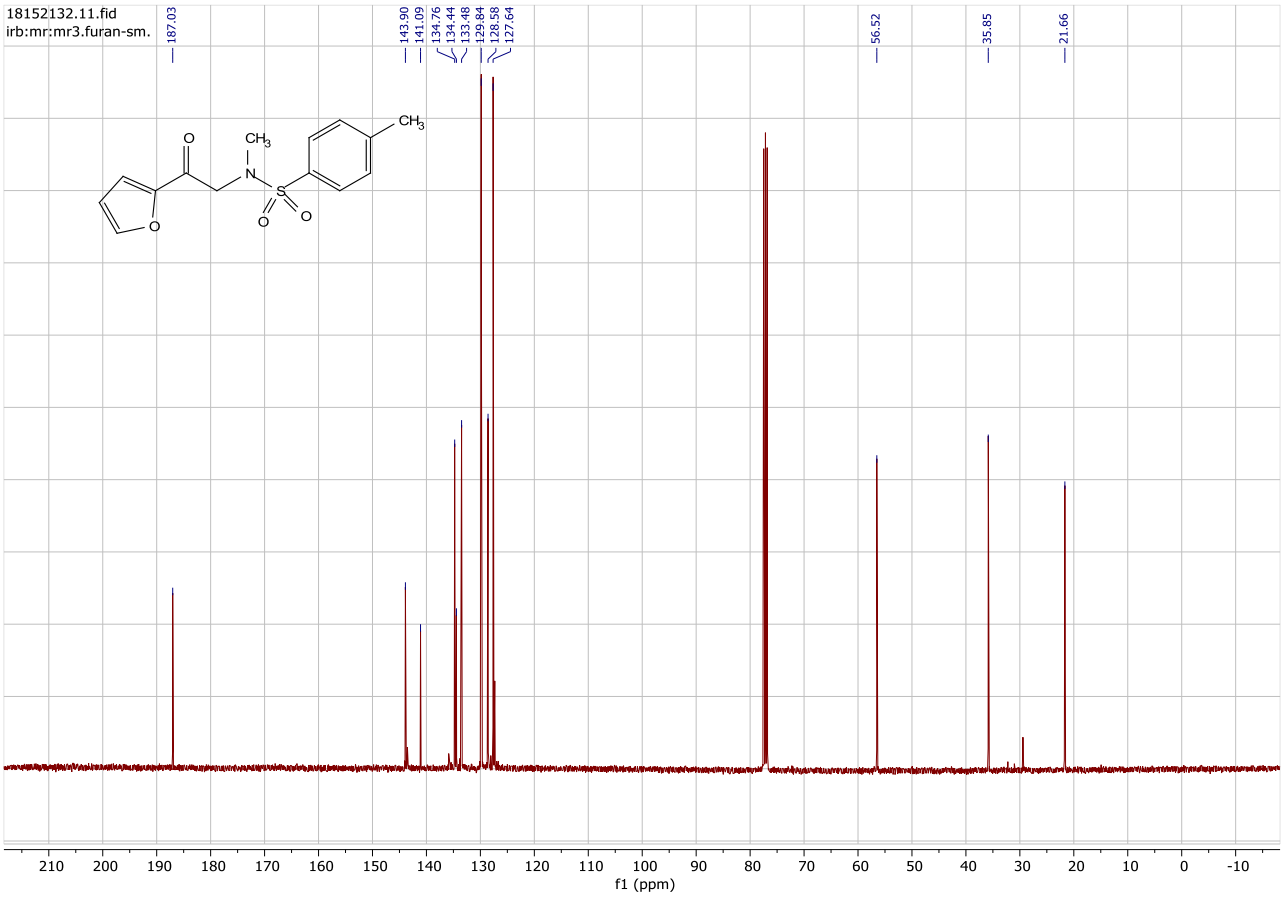
Compound 1-136a ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



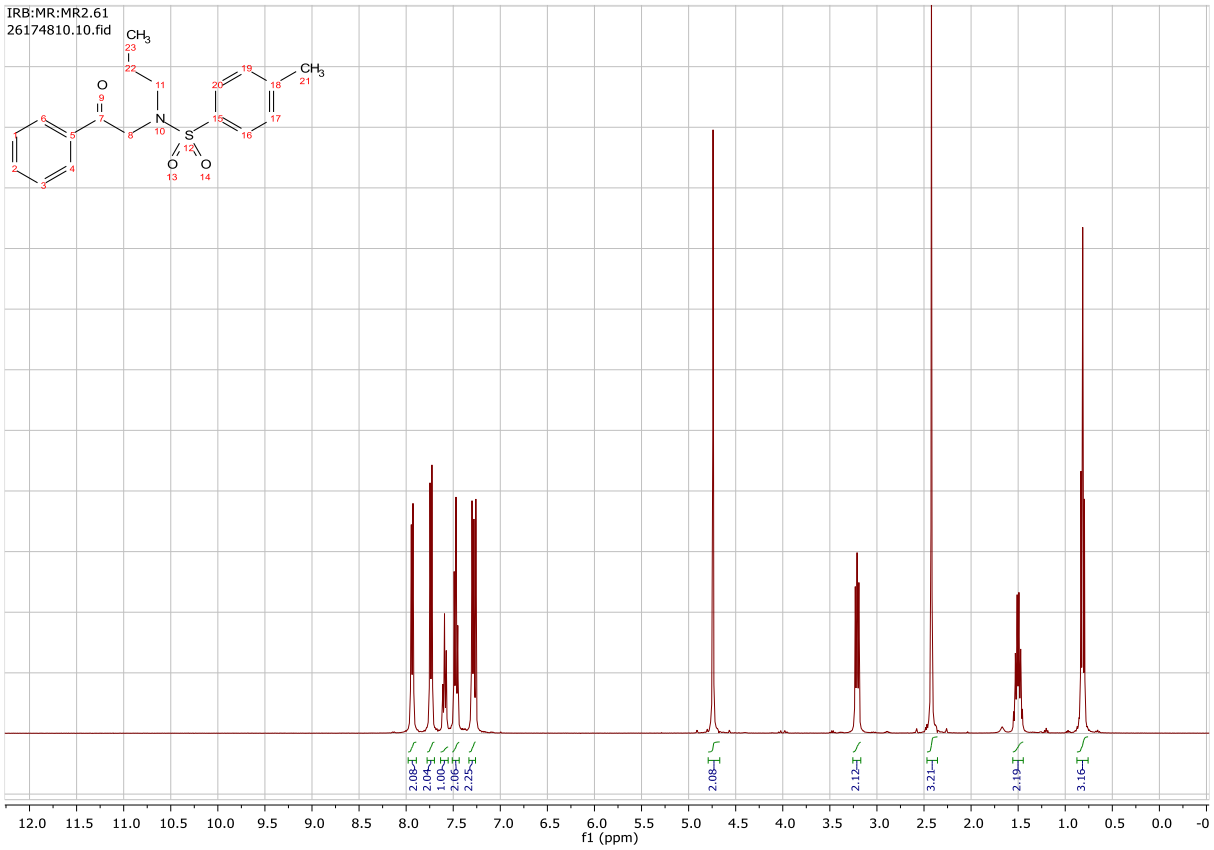
Compound 1-137a ^{1}H NMR (101 MHz, $CDCl_3$)



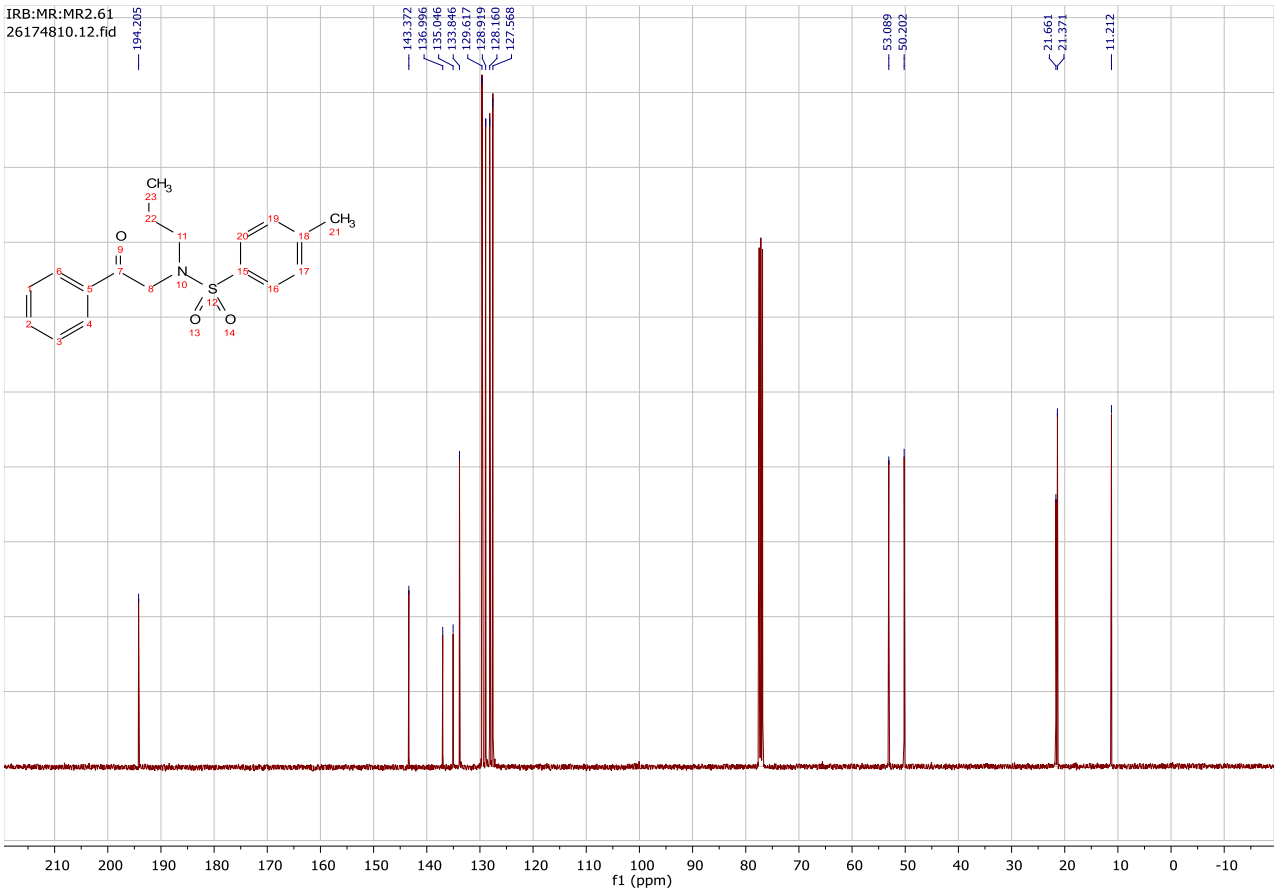
Compound 1-137a $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



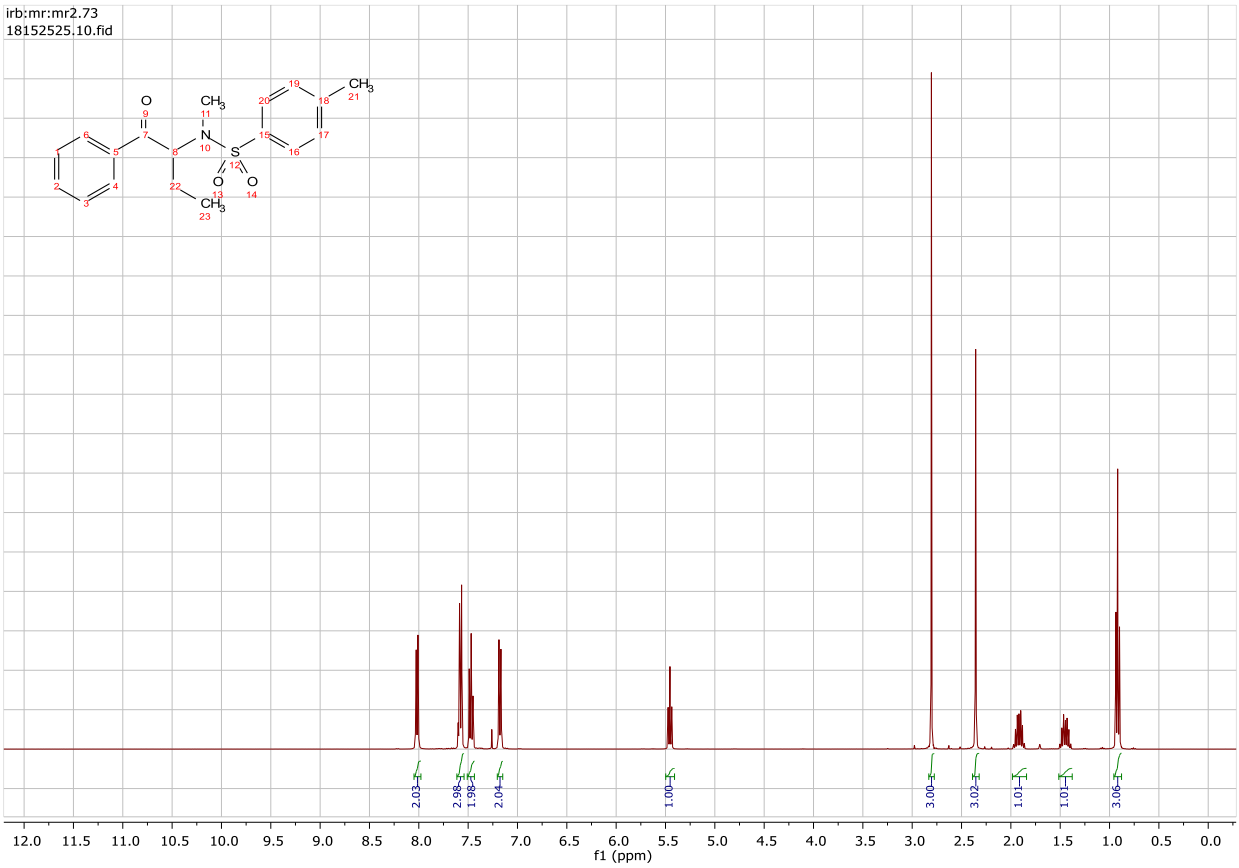
Compound 1-139a ^{1}H NMR (101 MHz, $CDCl_3$)



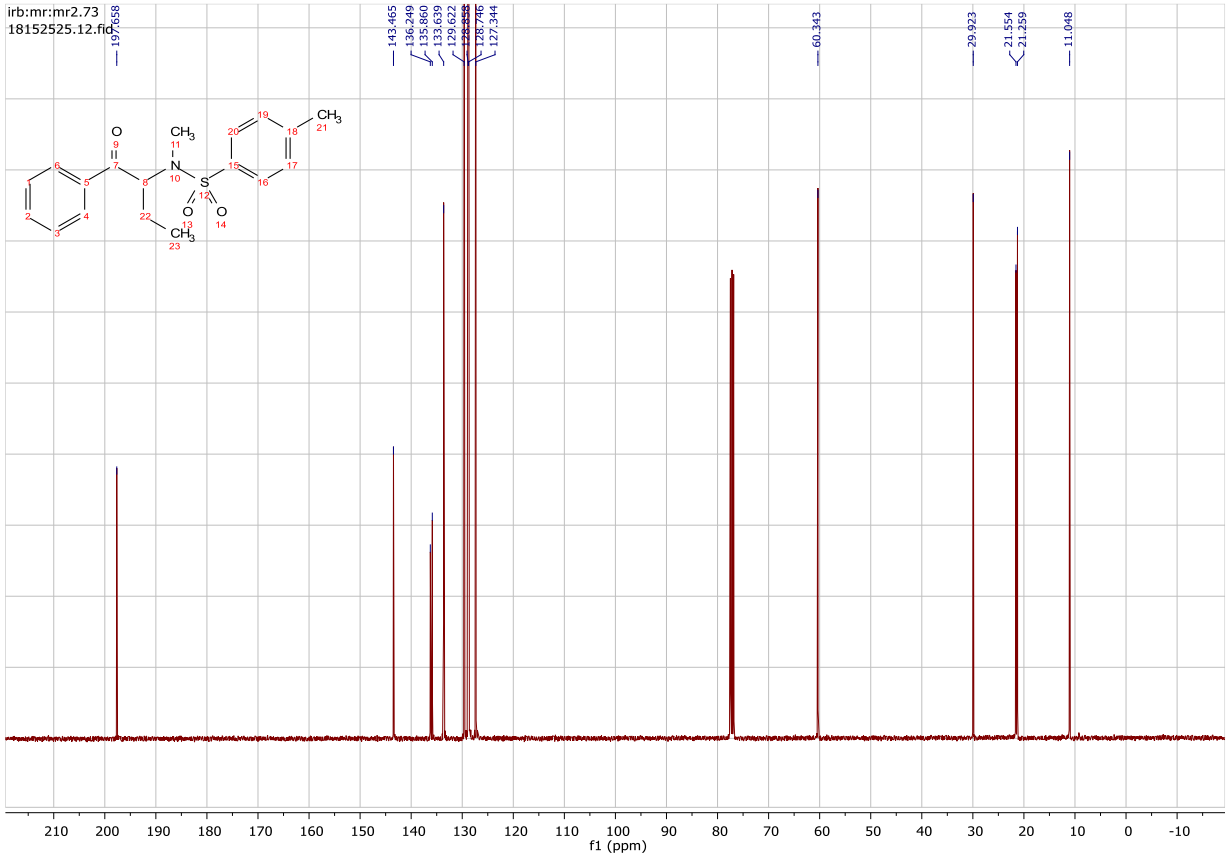
Compound 1-139a $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



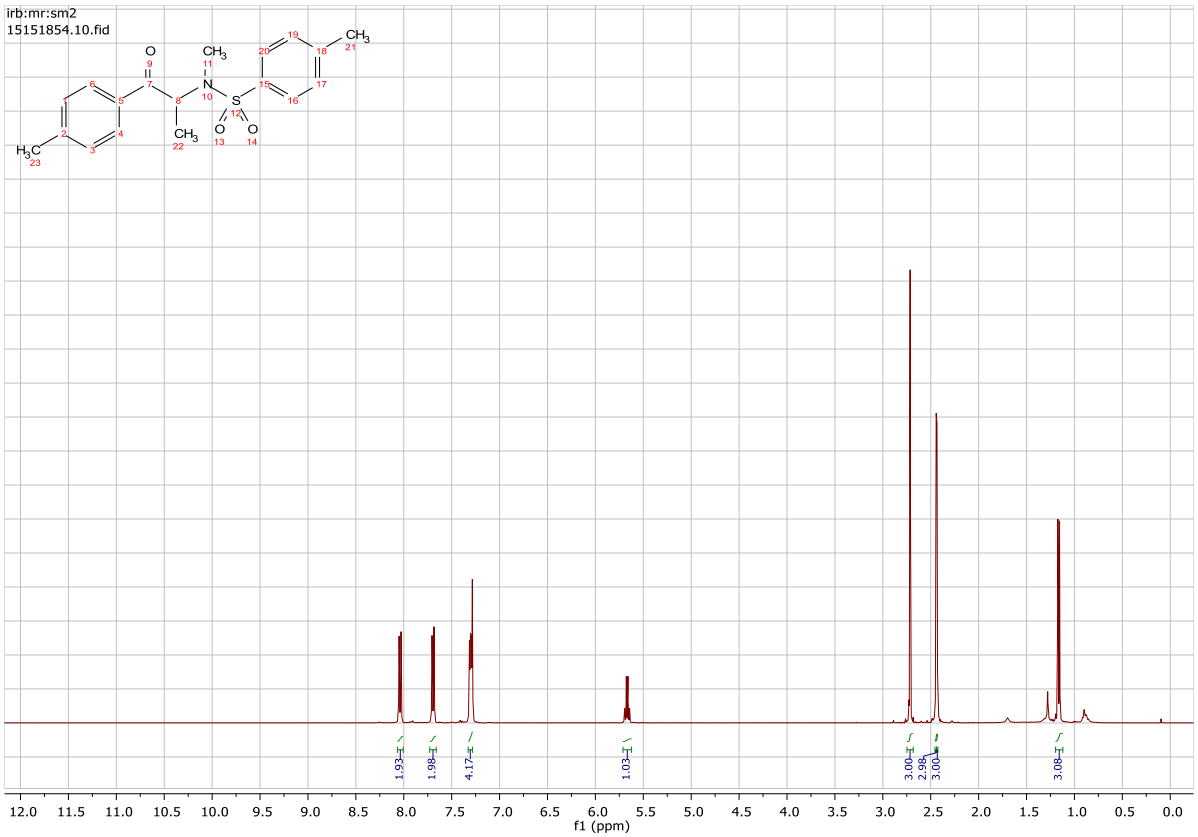
Compound 1-140a ^{1}H NMR (101 MHz, $CDCl_3$)



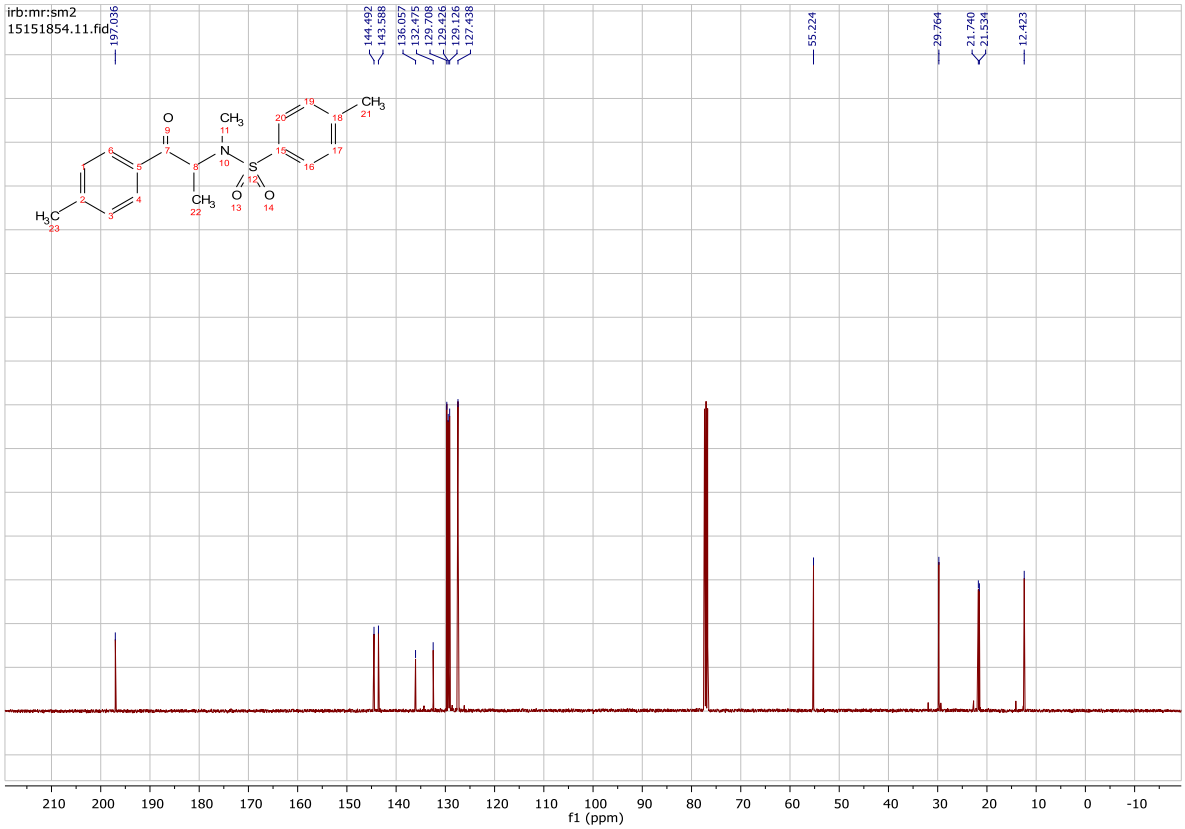
Compound 1-140a ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



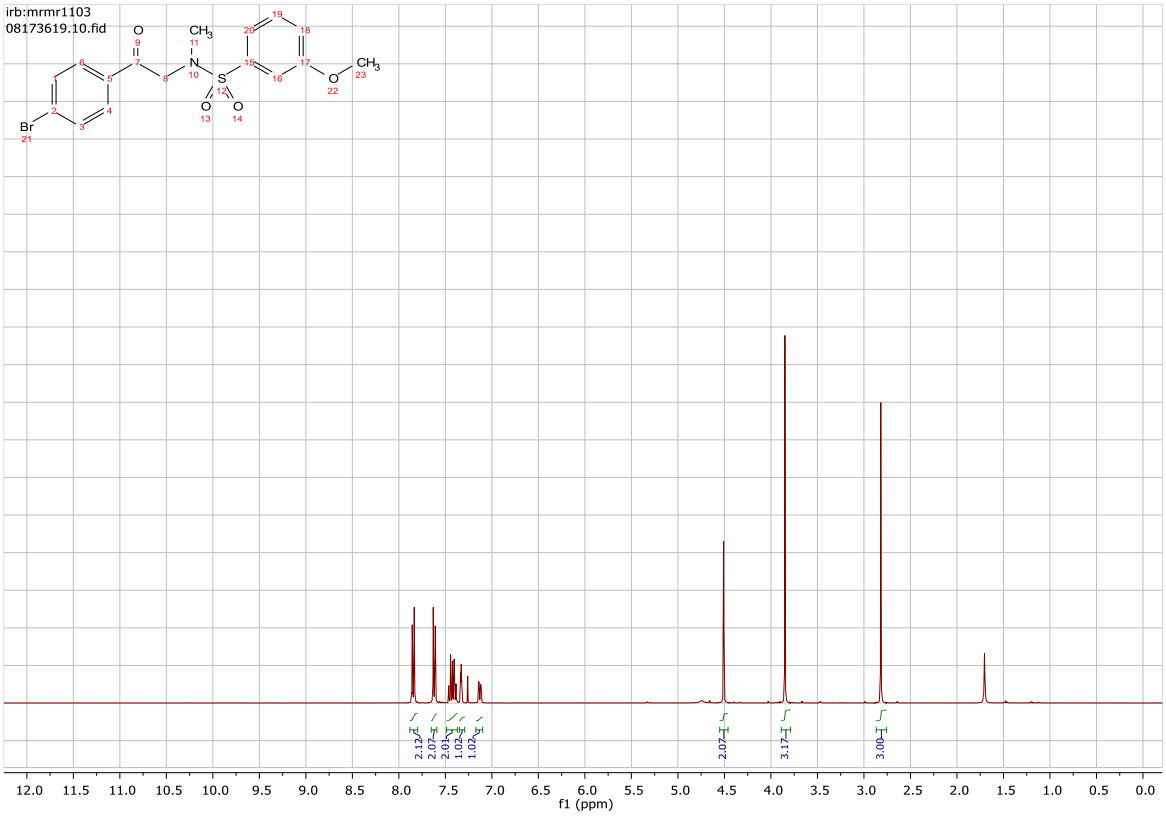
Compound 1-142a ^{1}H NMR (101 MHz, $CDCl_3$)



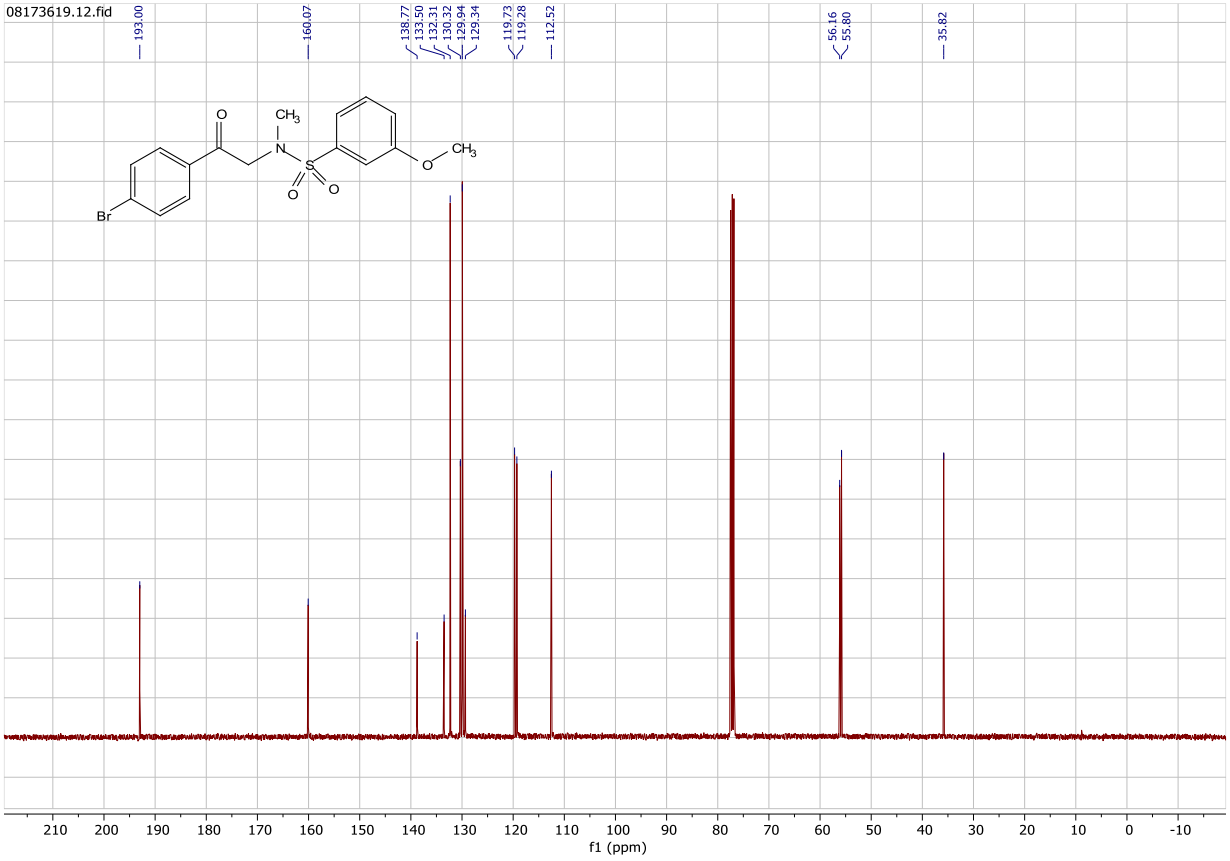
Compound 1-142a $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



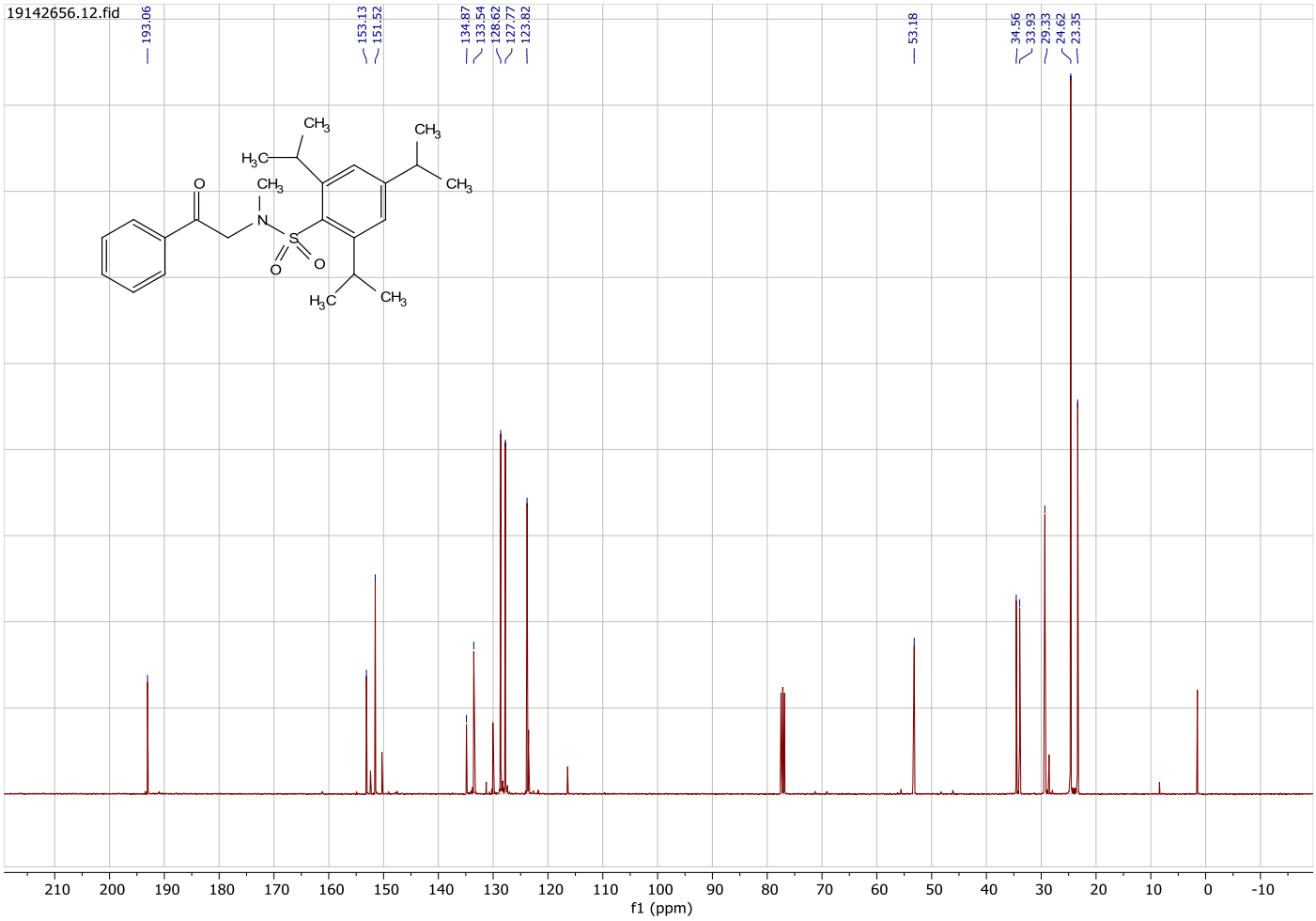
Compound 1-143a ^{1}H NMR (101 MHz, $CDCl_3$)



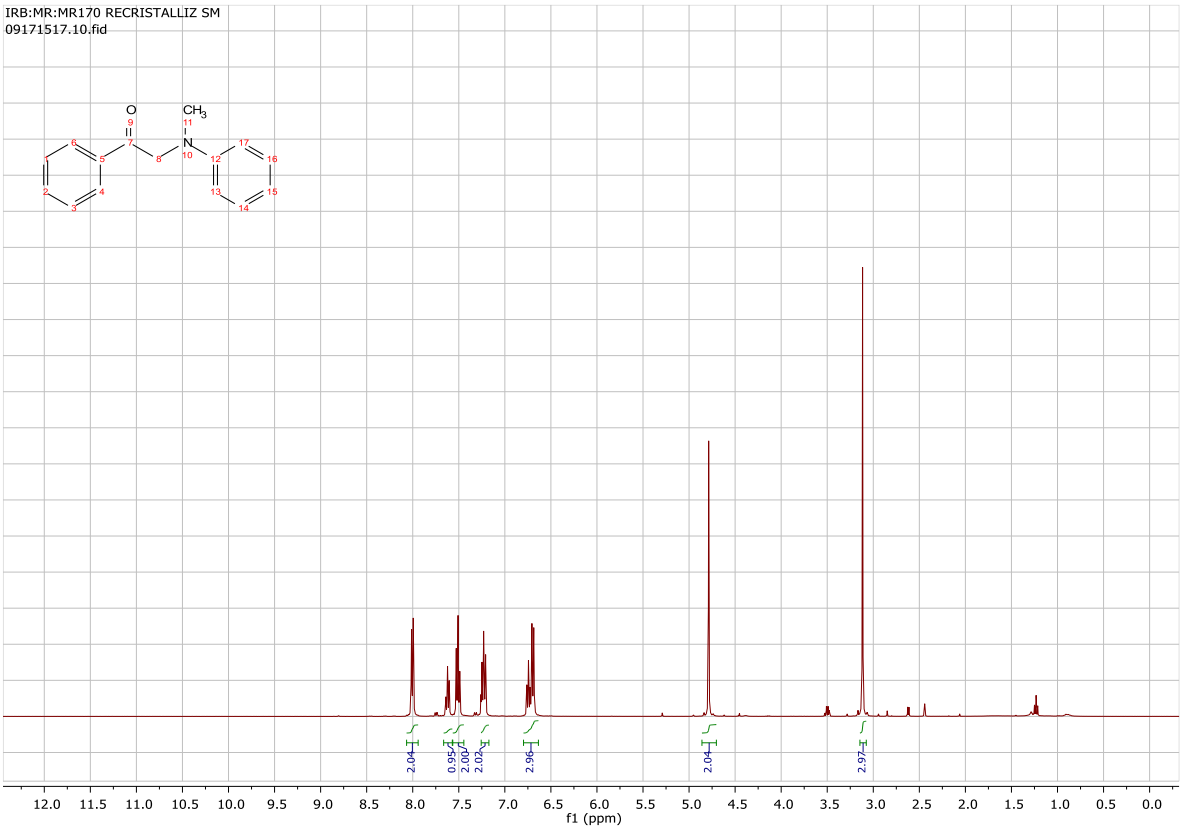
Compound 1-143a $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



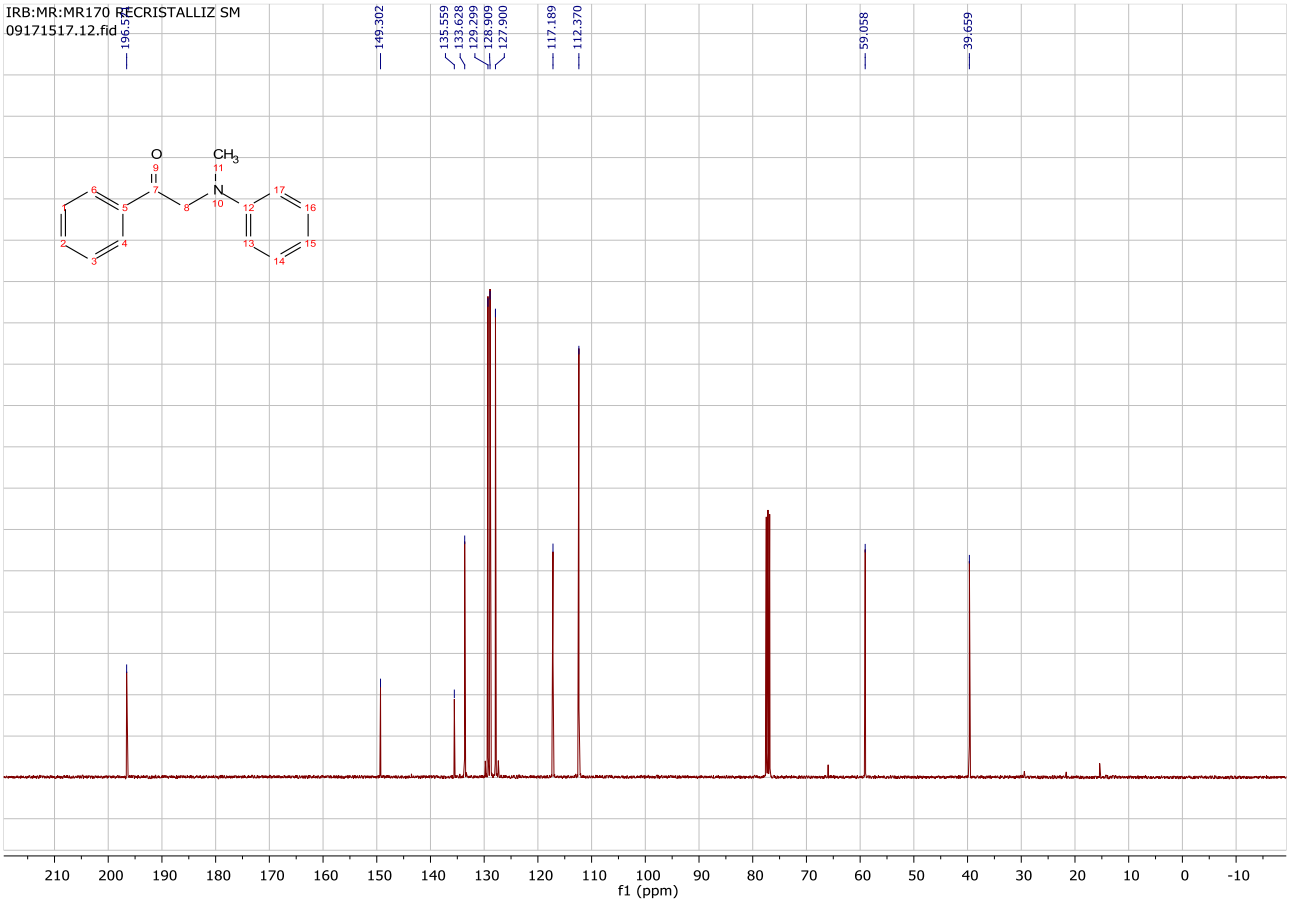
Compound 1-144a ^{1}H NMR (101 MHz, $CDCl_3$)



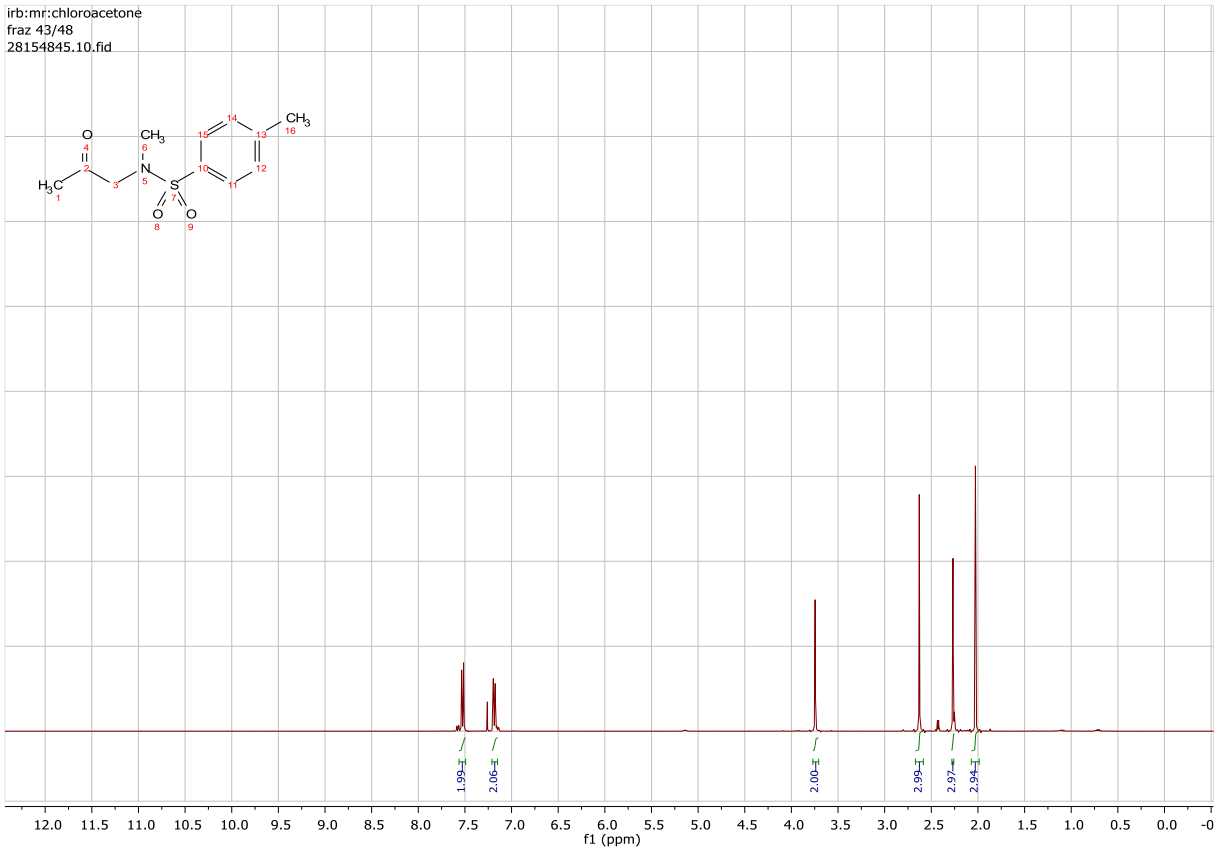
Compound 1-146a ^{1}H NMR (101 MHz, $CDCl_3$)



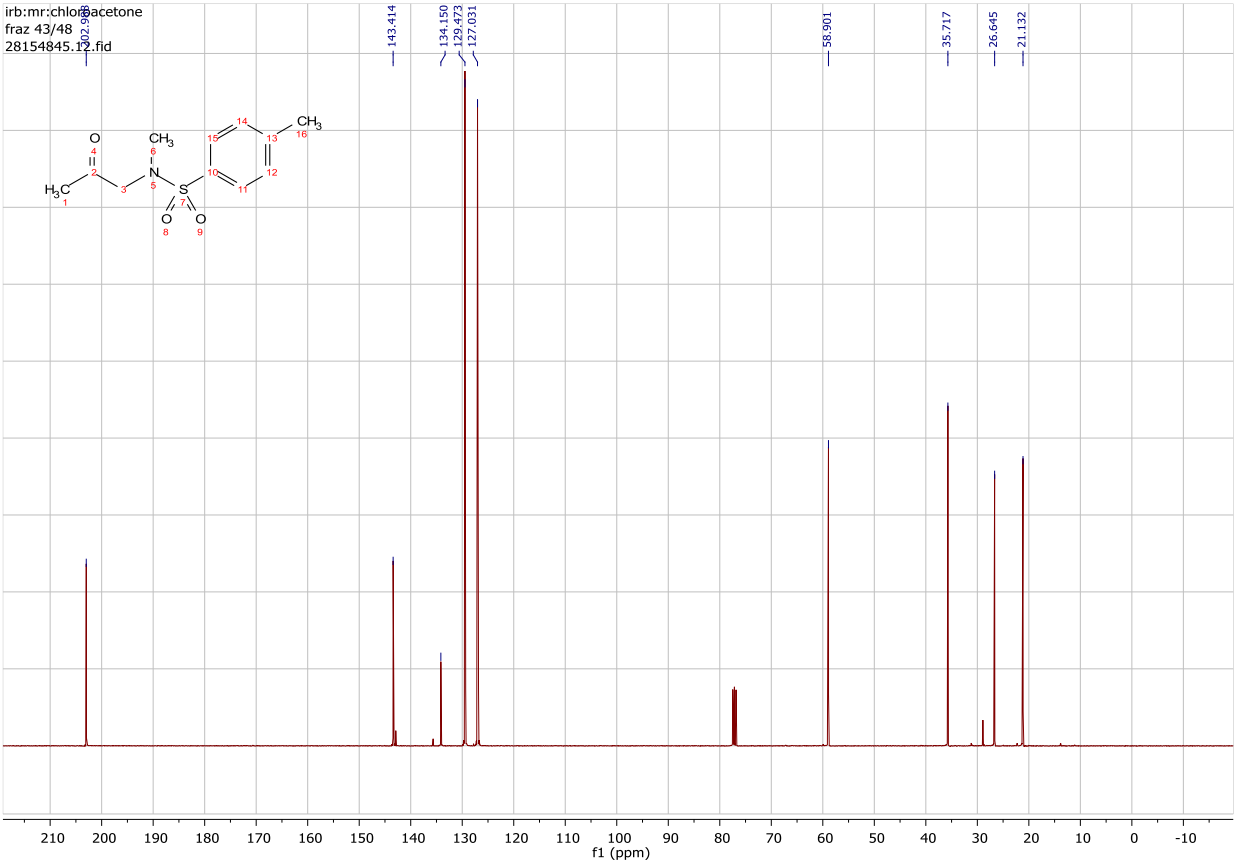
Compound 1-146a $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



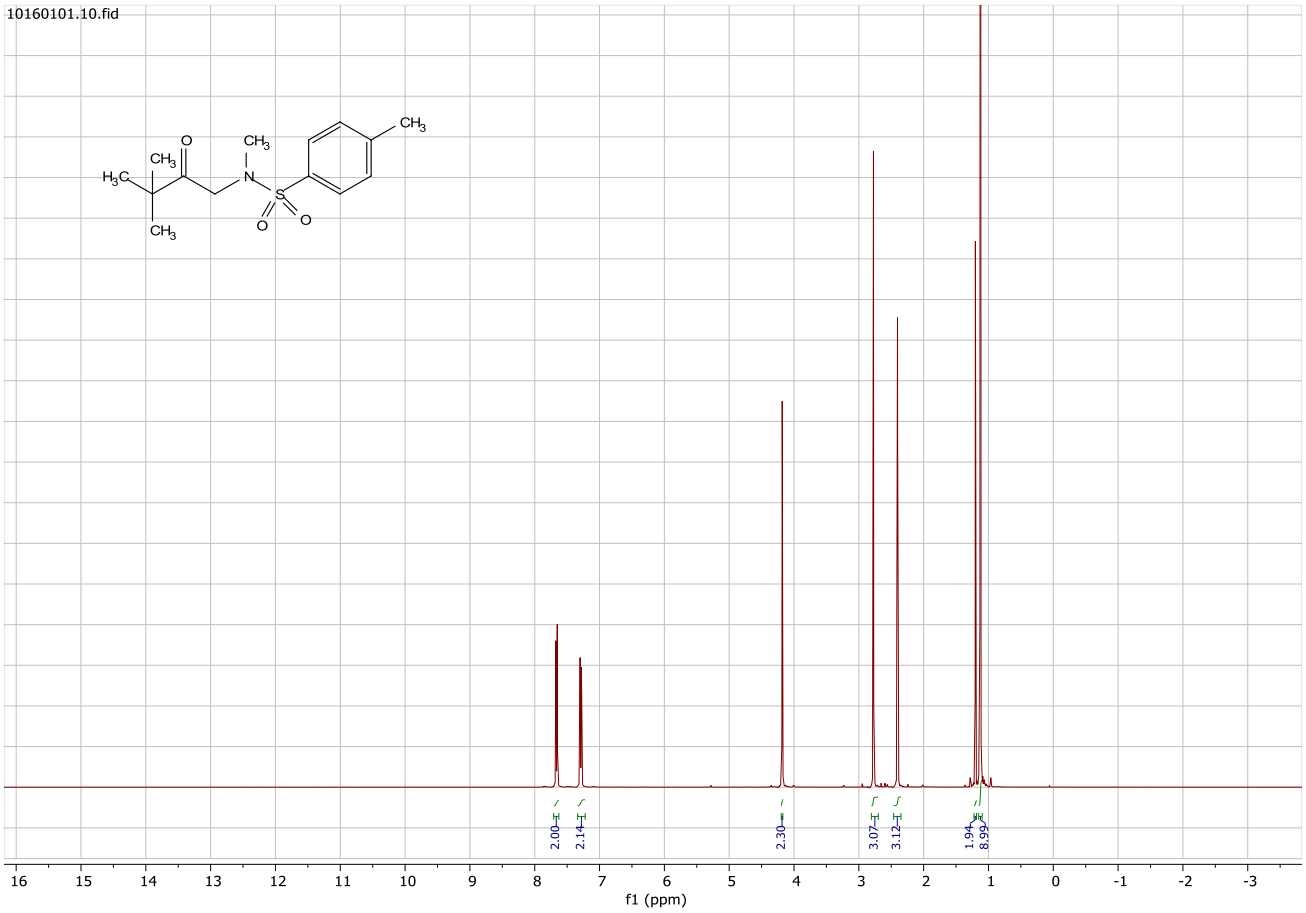
Compound 1-151a ^{1}H NMR (101 MHz, $CDCl_3$)



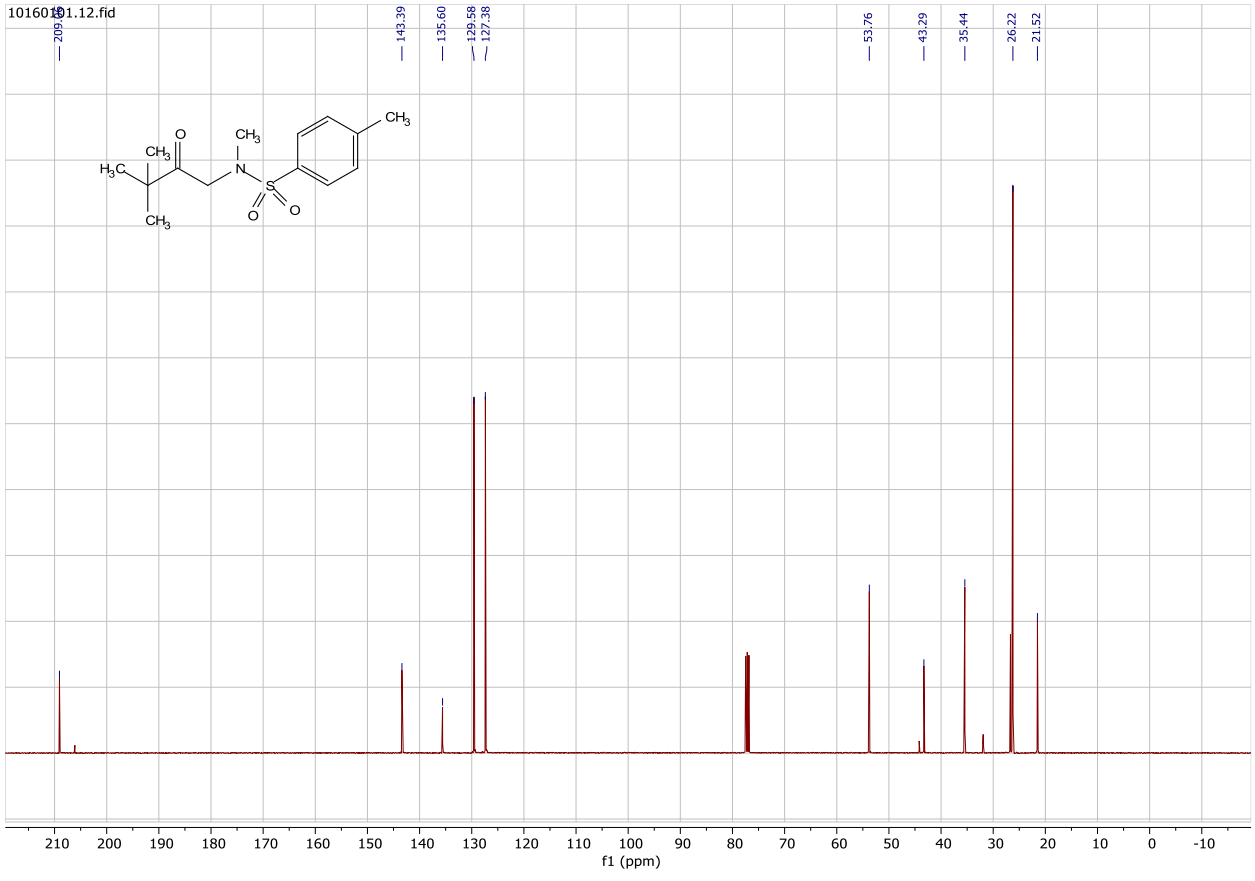
Compound 1-151a ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



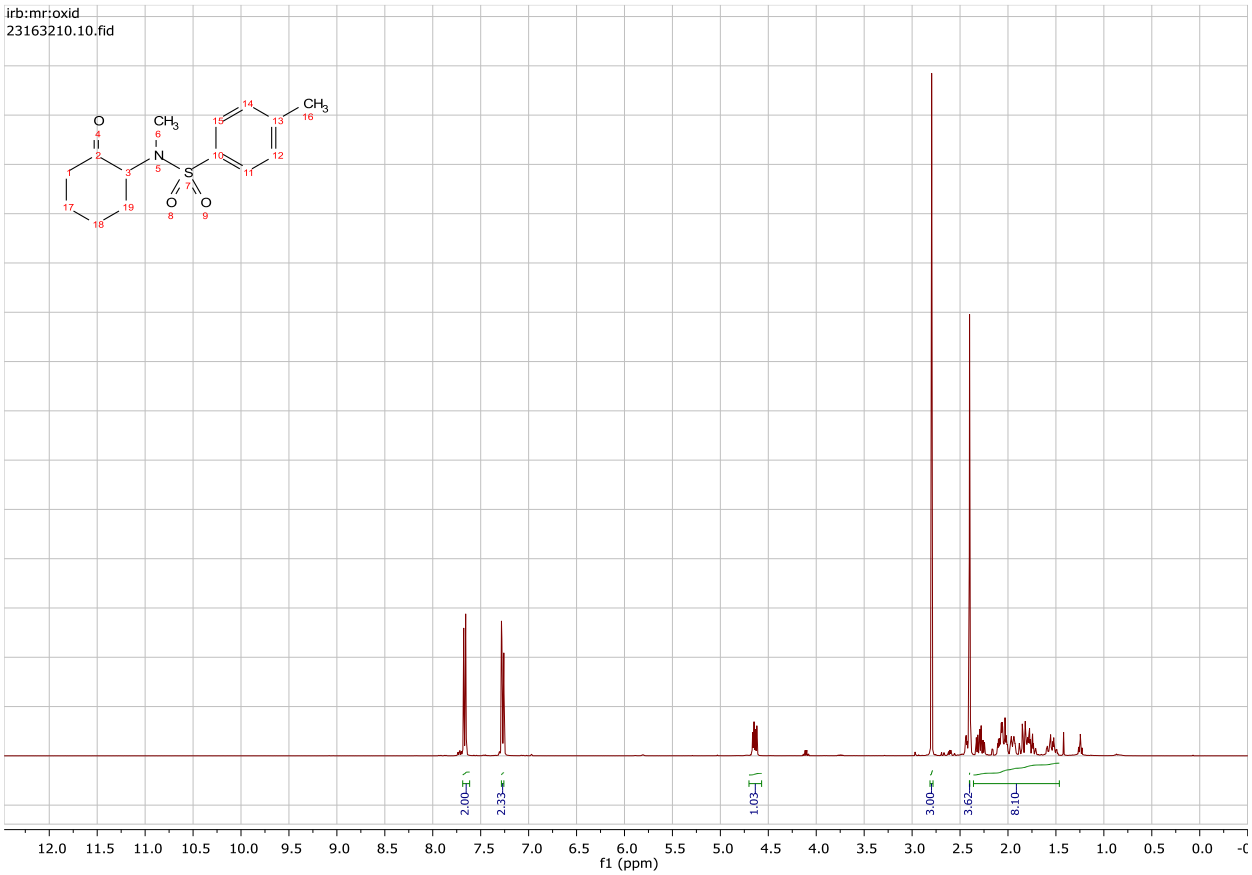
Compound 1-152a ^{1}H NMR (101 MHz, $CDCl_3$)



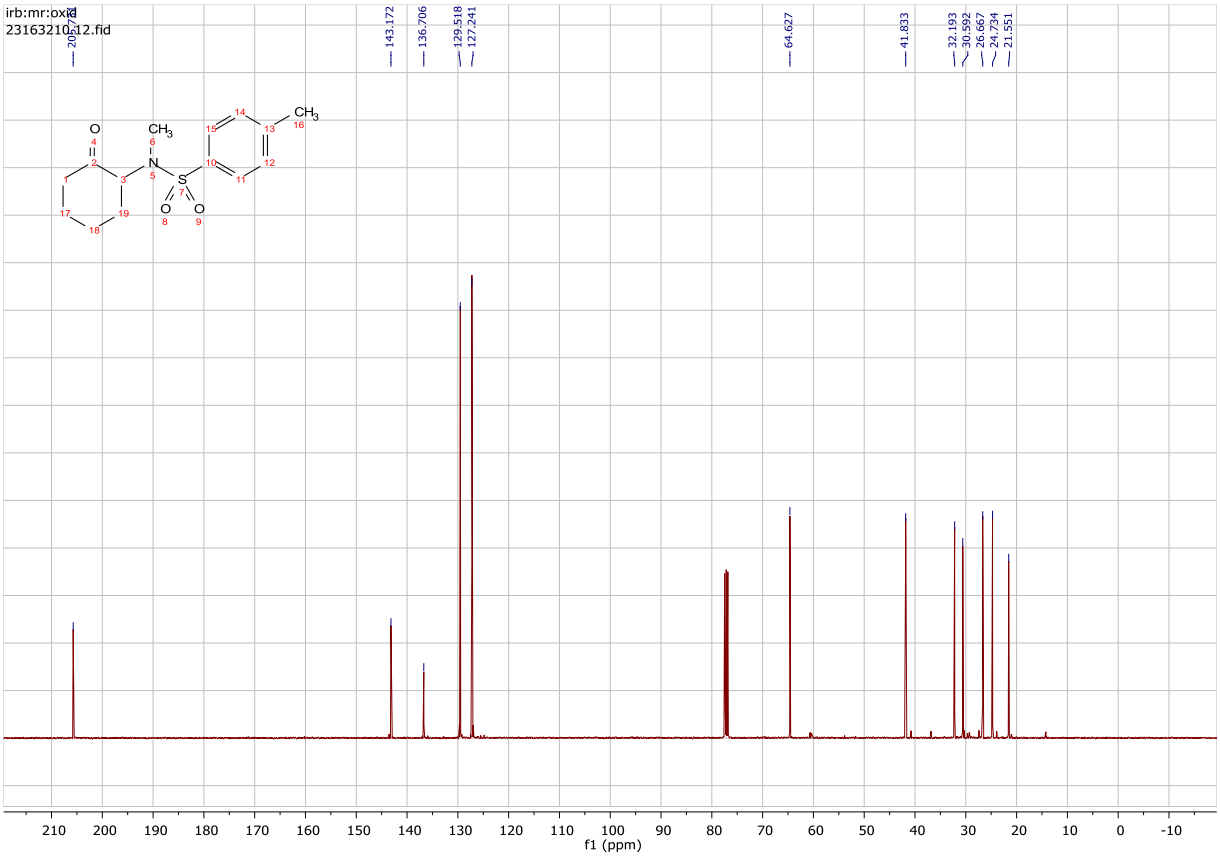
Compound 1-152a ^{13}C{1H} NMR (101 MHz, $CDCl_3$)



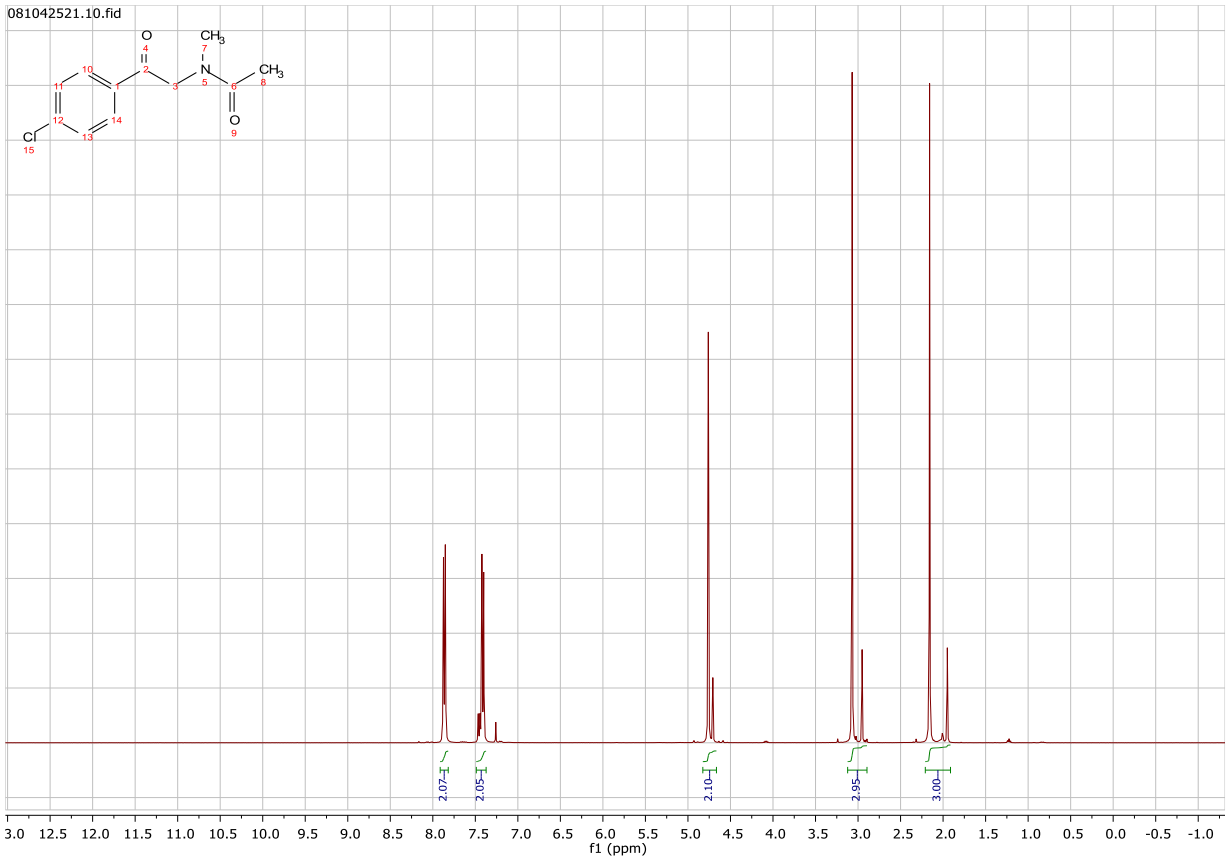
Compound 1-150a ^{1}H NMR (101 MHz, $CDCl_3$)



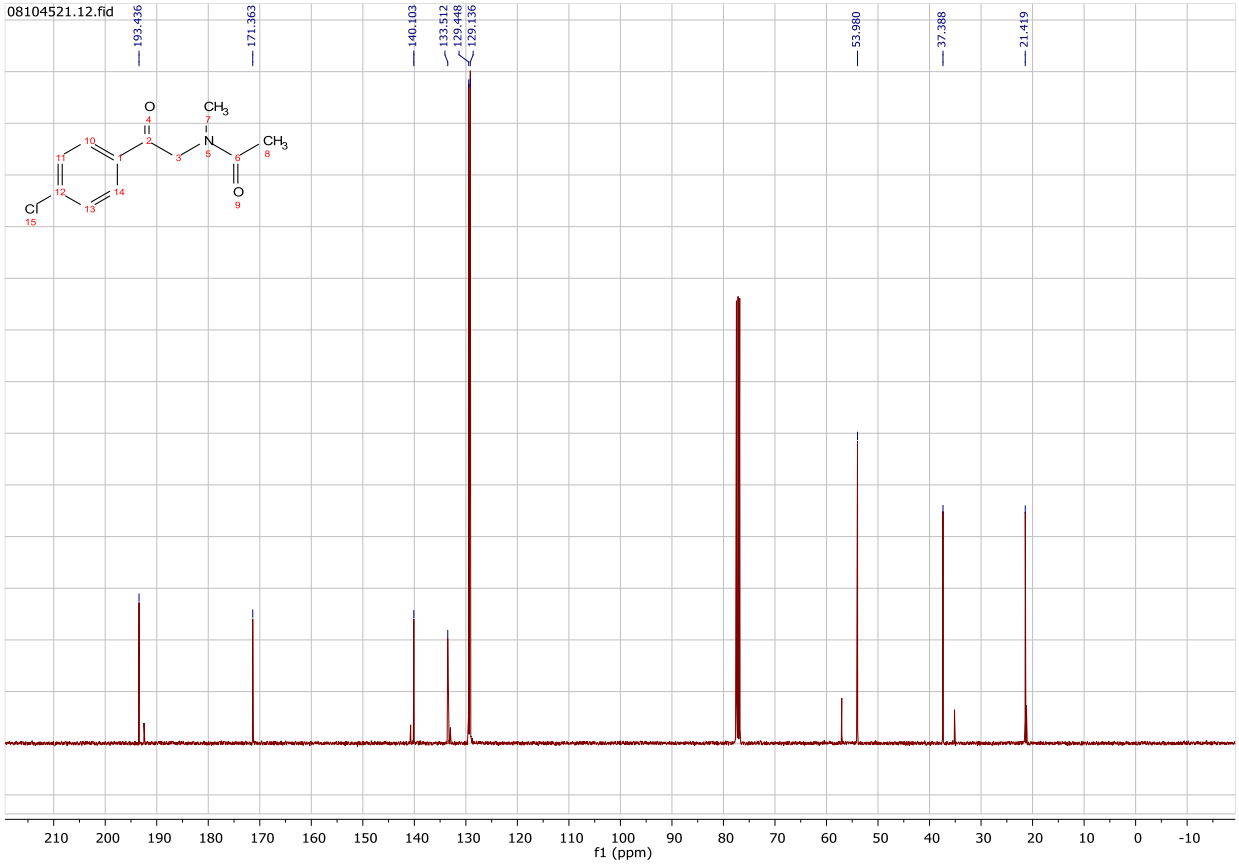
Compound 1-150a $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



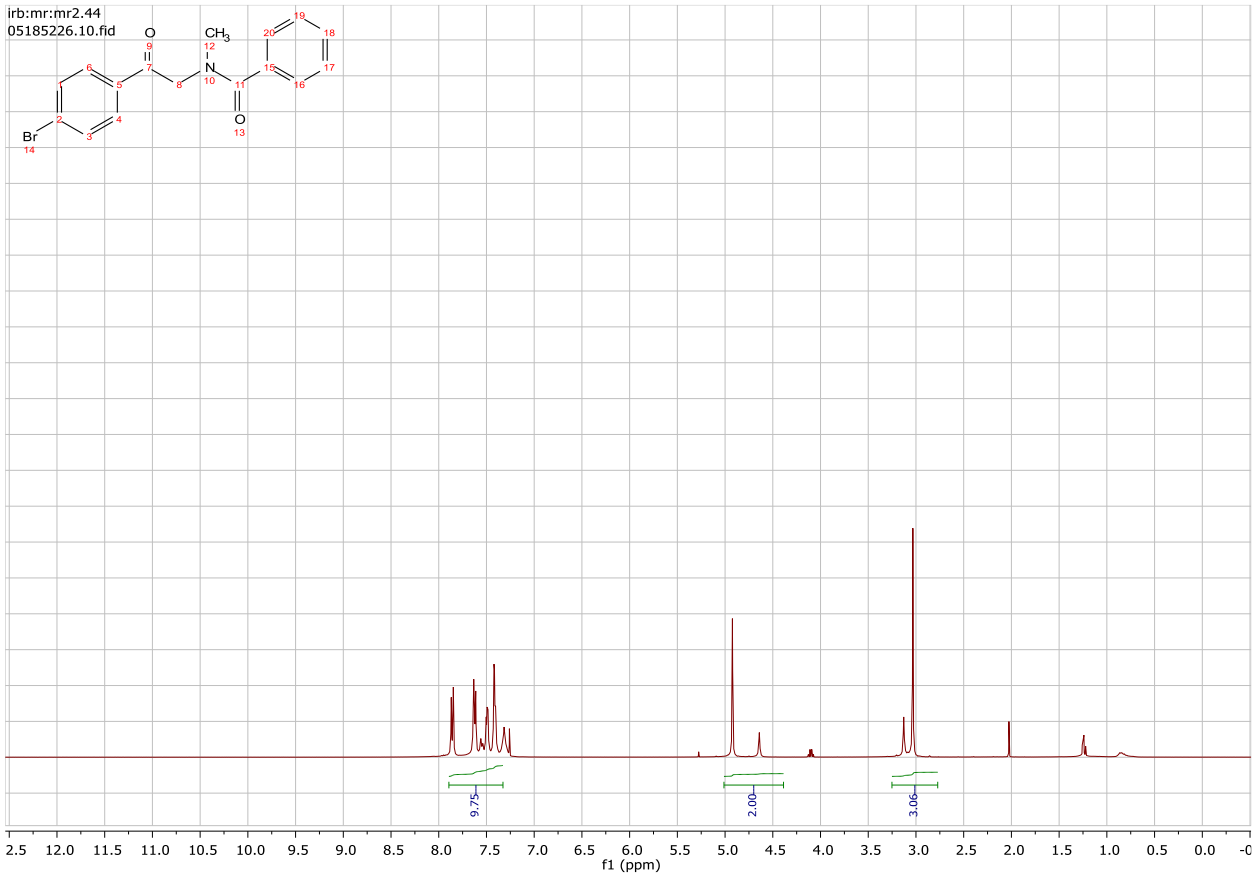
Compound 1-156a ^{1}H NMR (101 MHz, $CDCl_3$)



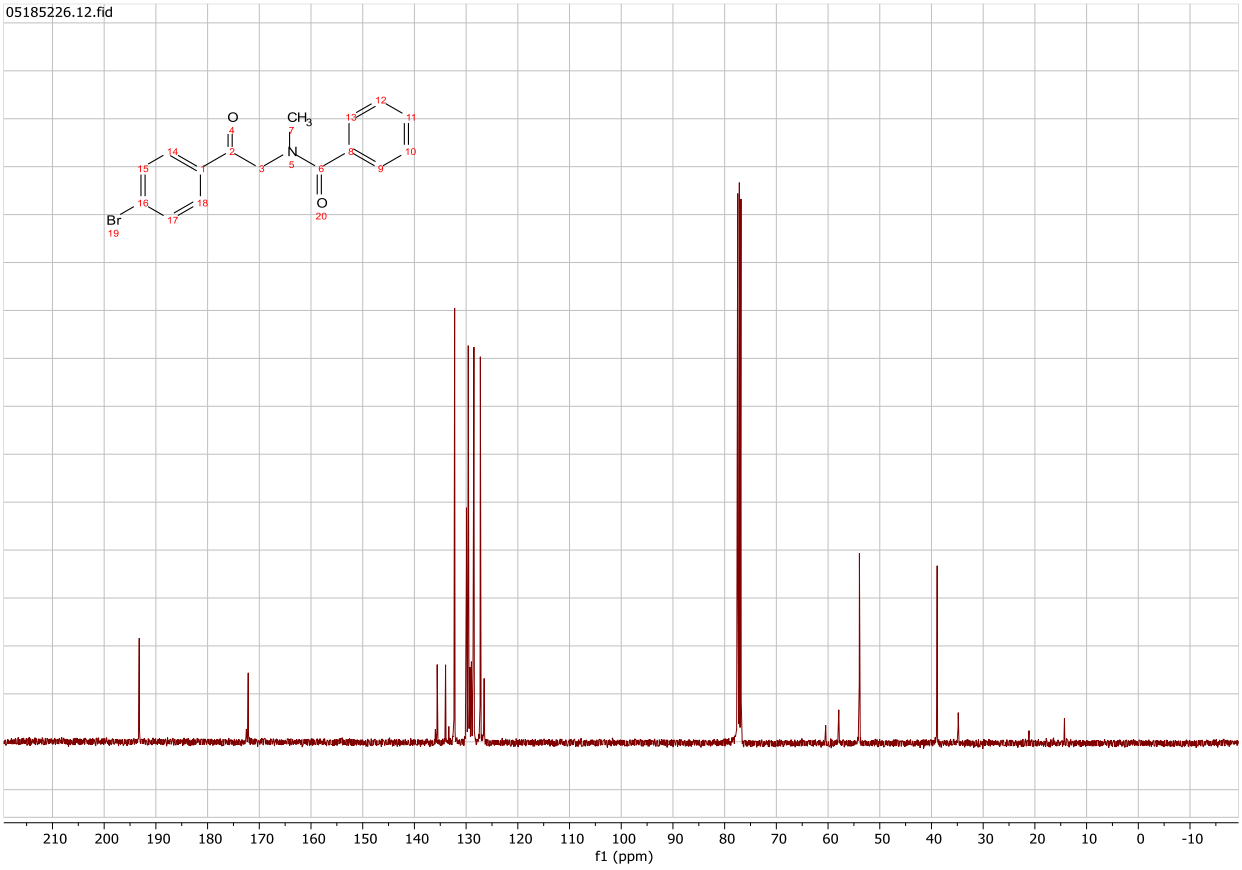
Compound 1-156a ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



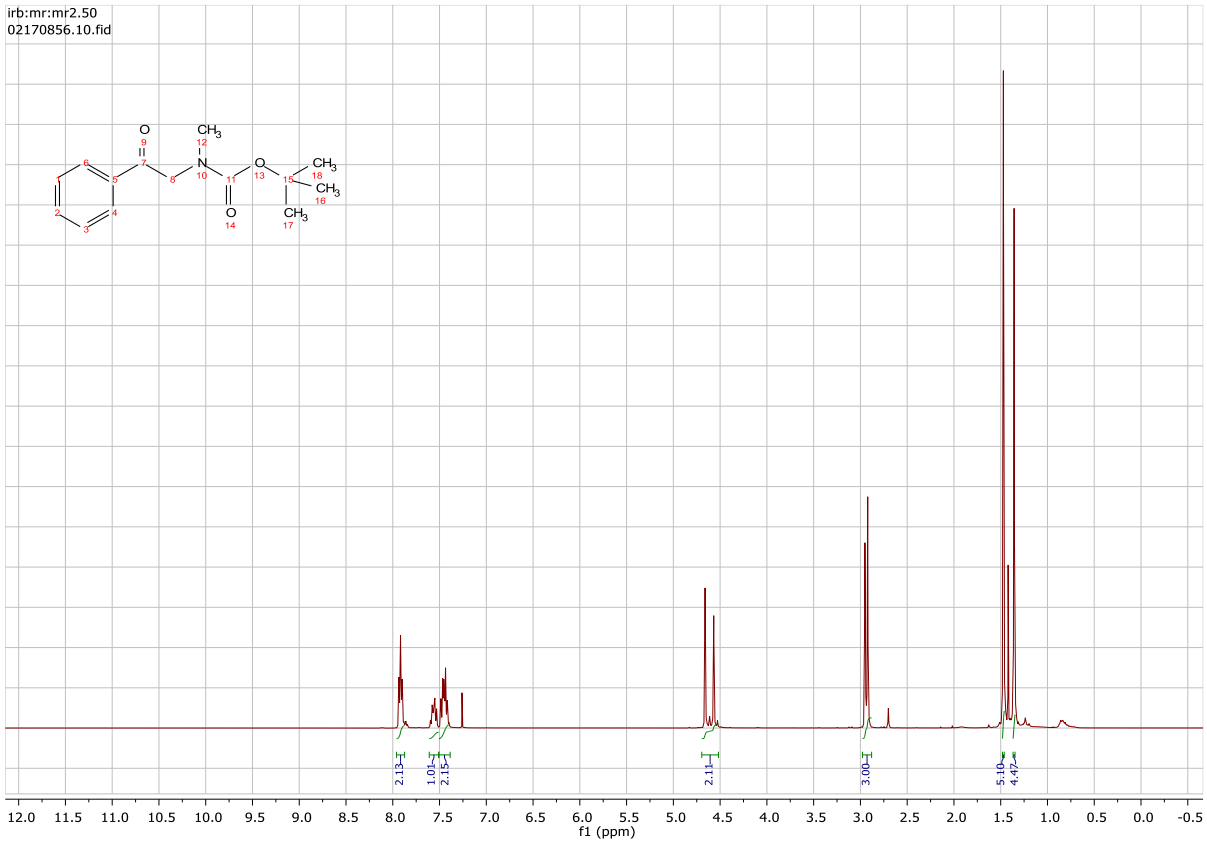
Compound 1-157a ^{1}H NMR (101 MHz, $CDCl_3$)



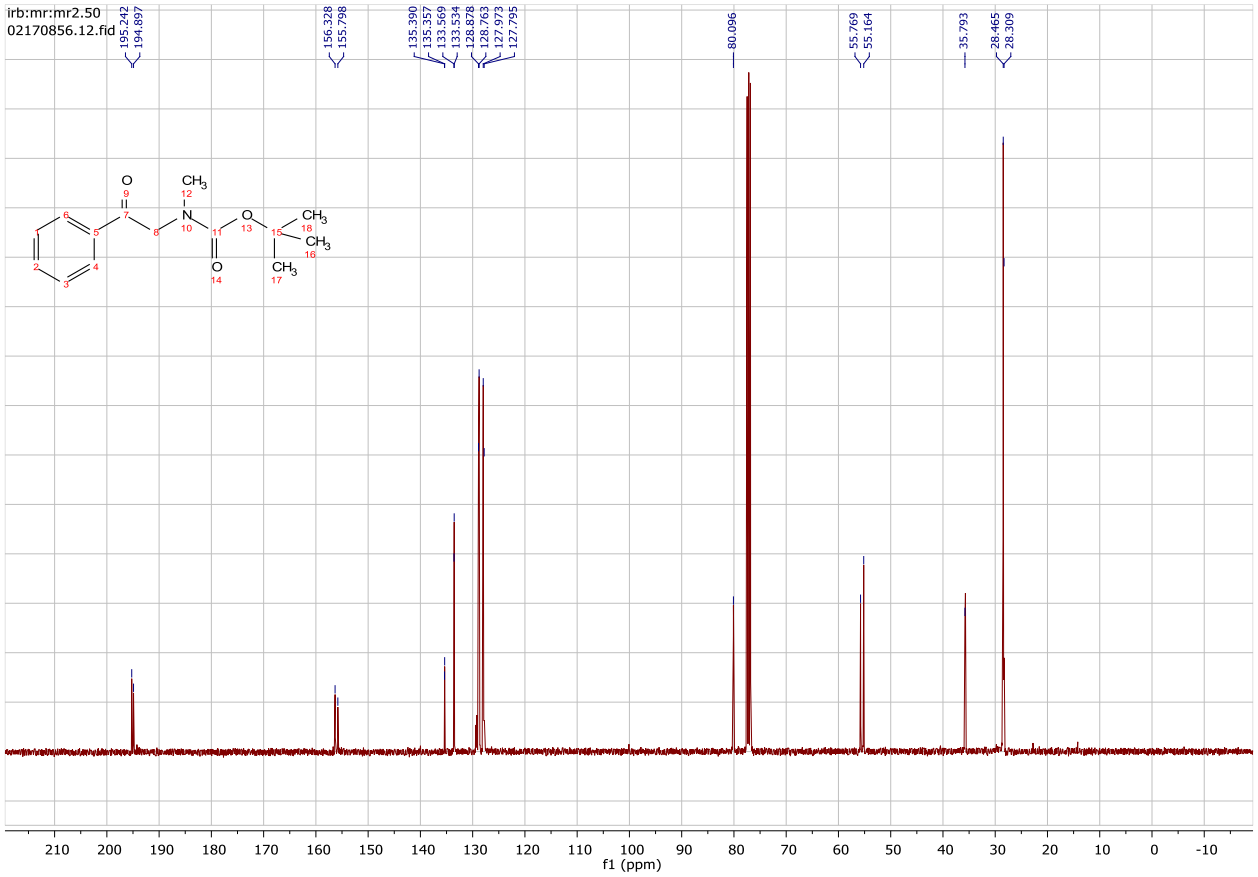
Compound 1-157a ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



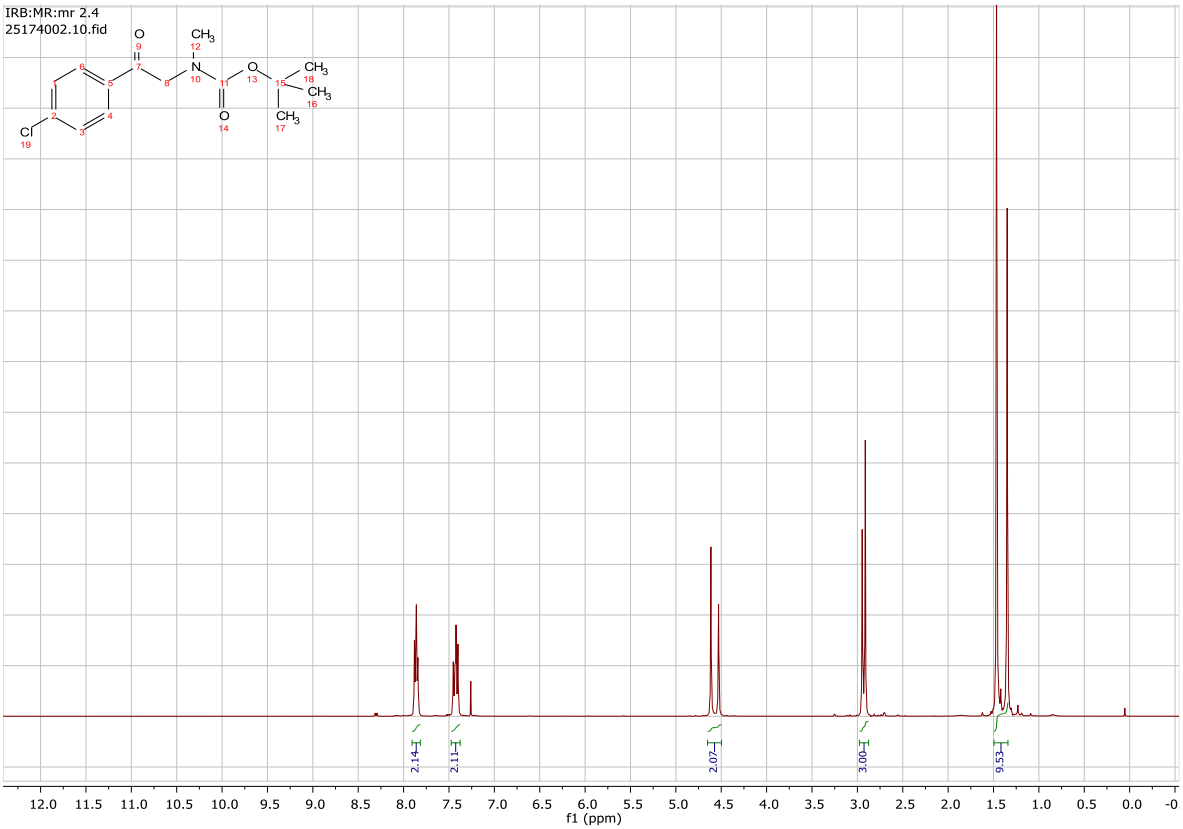
Compound 1-153a ^{1}H NMR (101 MHz, $CDCl_3$)



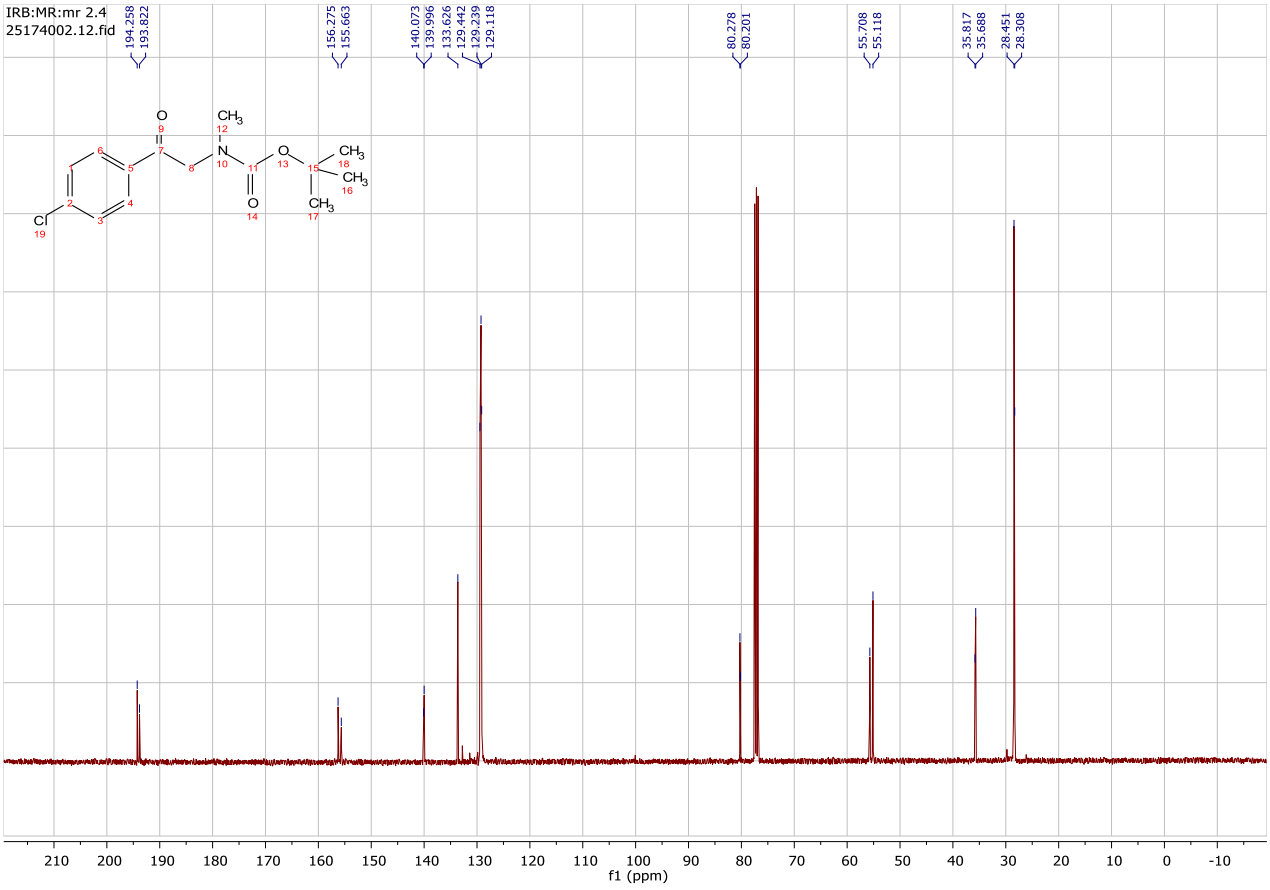
Compound 1-153a $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



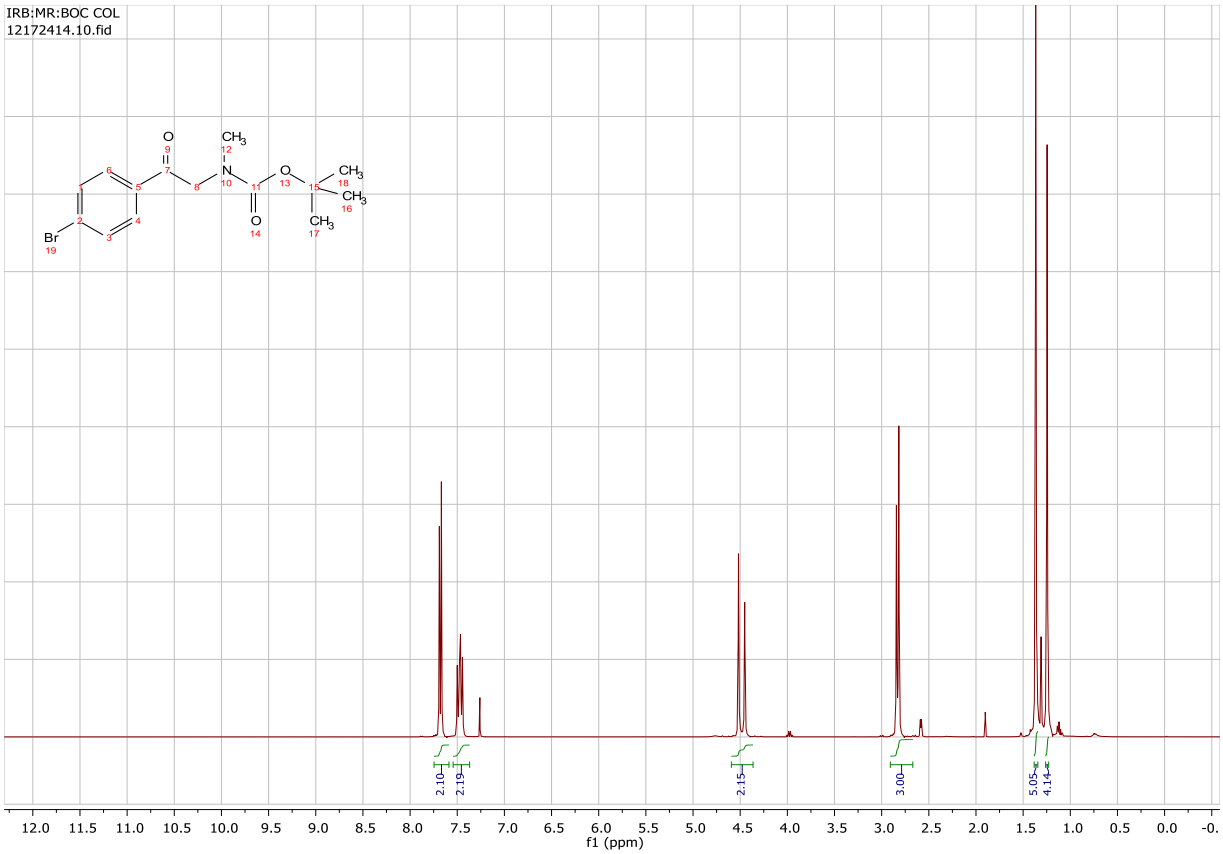
Compound 1-154a ^{1}H NMR (101 MHz, $CDCl_3$)



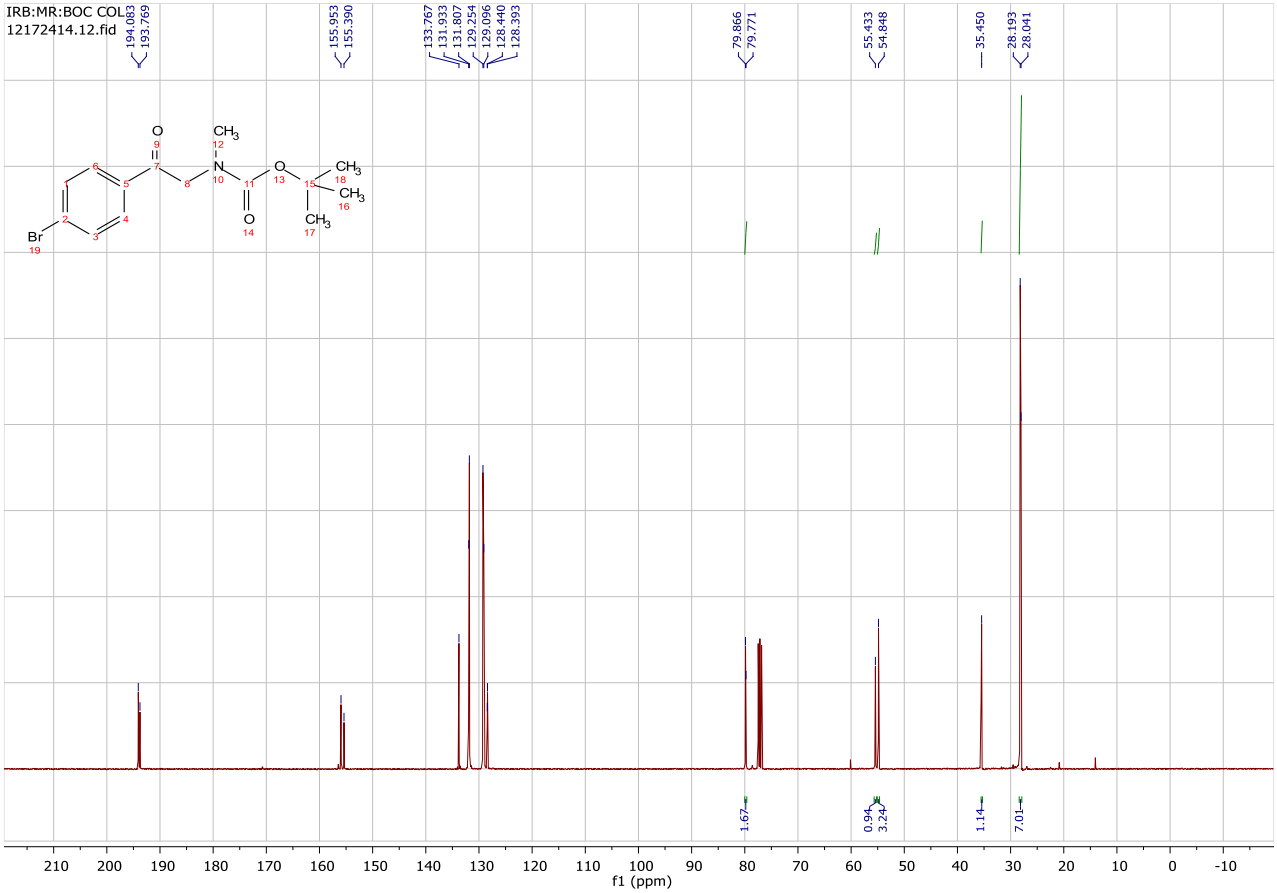
Compound 1-154a $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



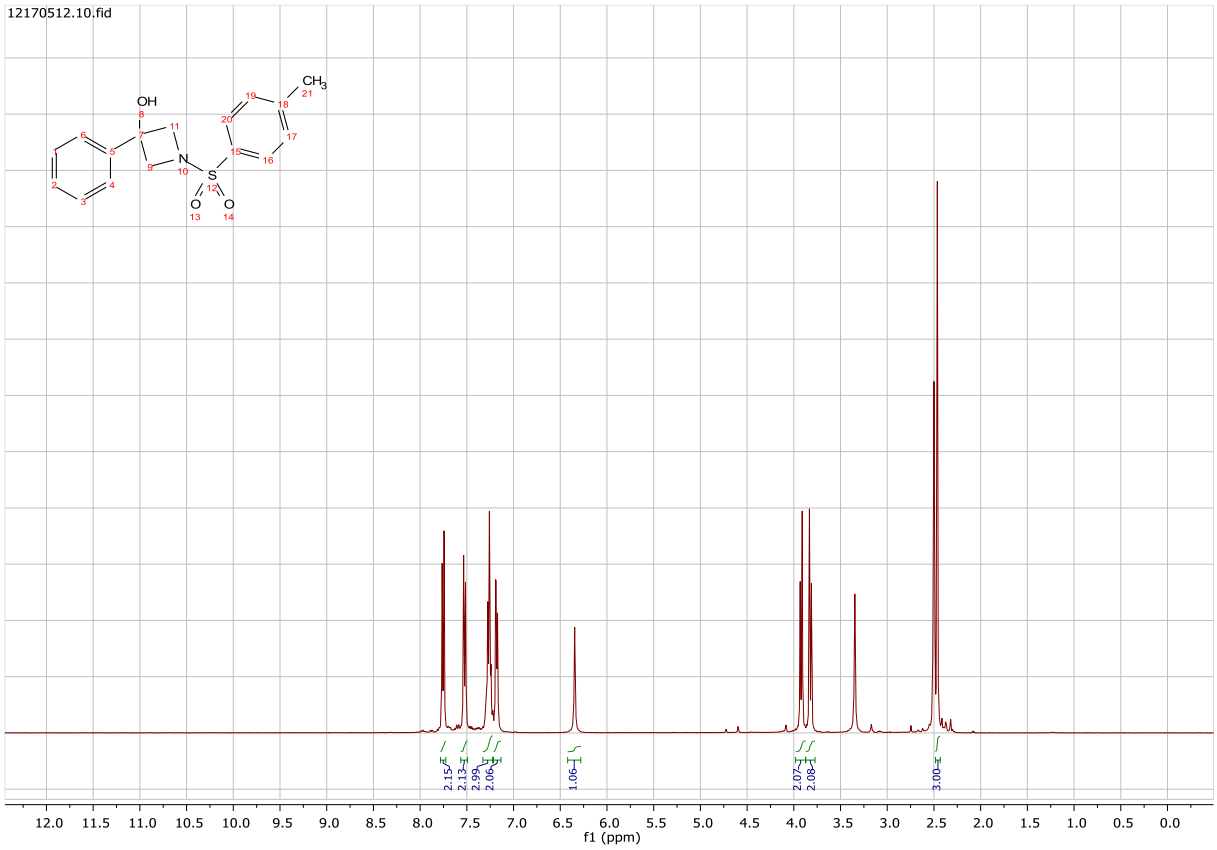
Compound 1-155a ^{1}H NMR (101 MHz, $CDCl_3$)



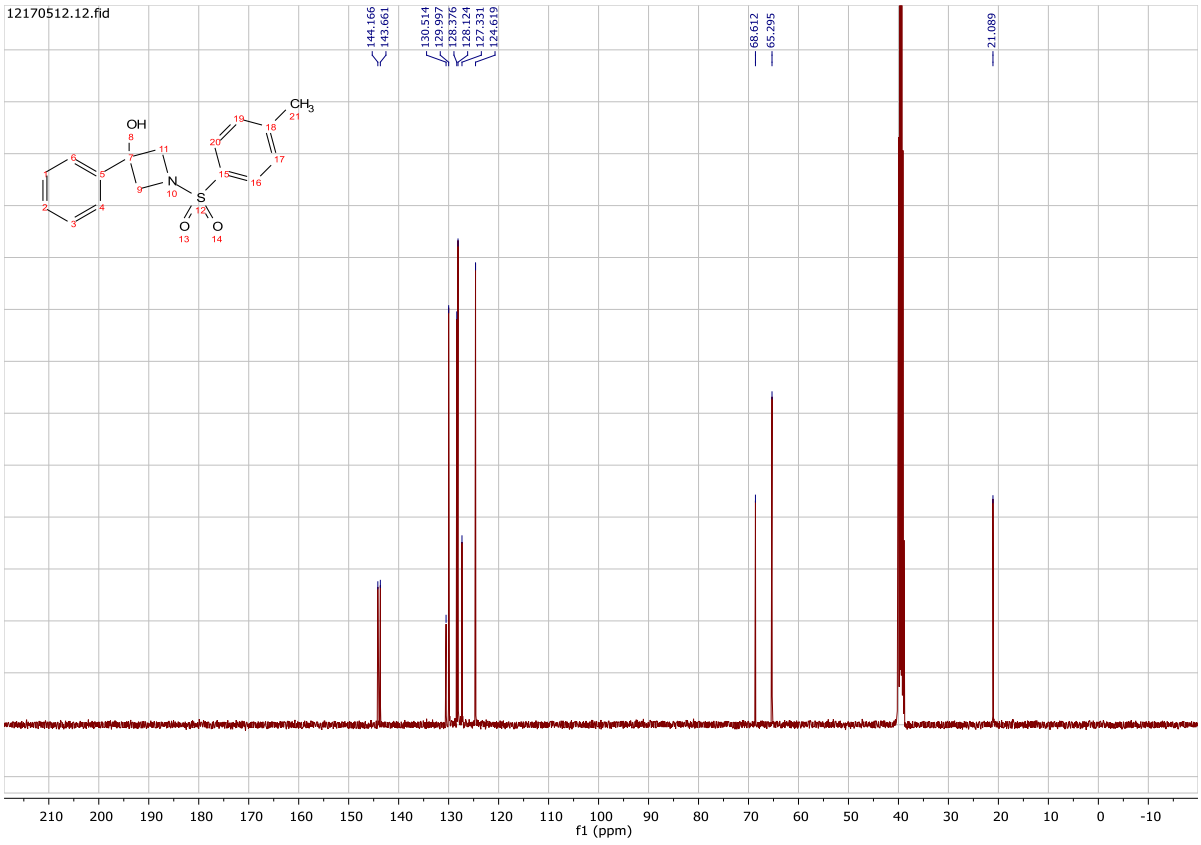
Compound 1-155a ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



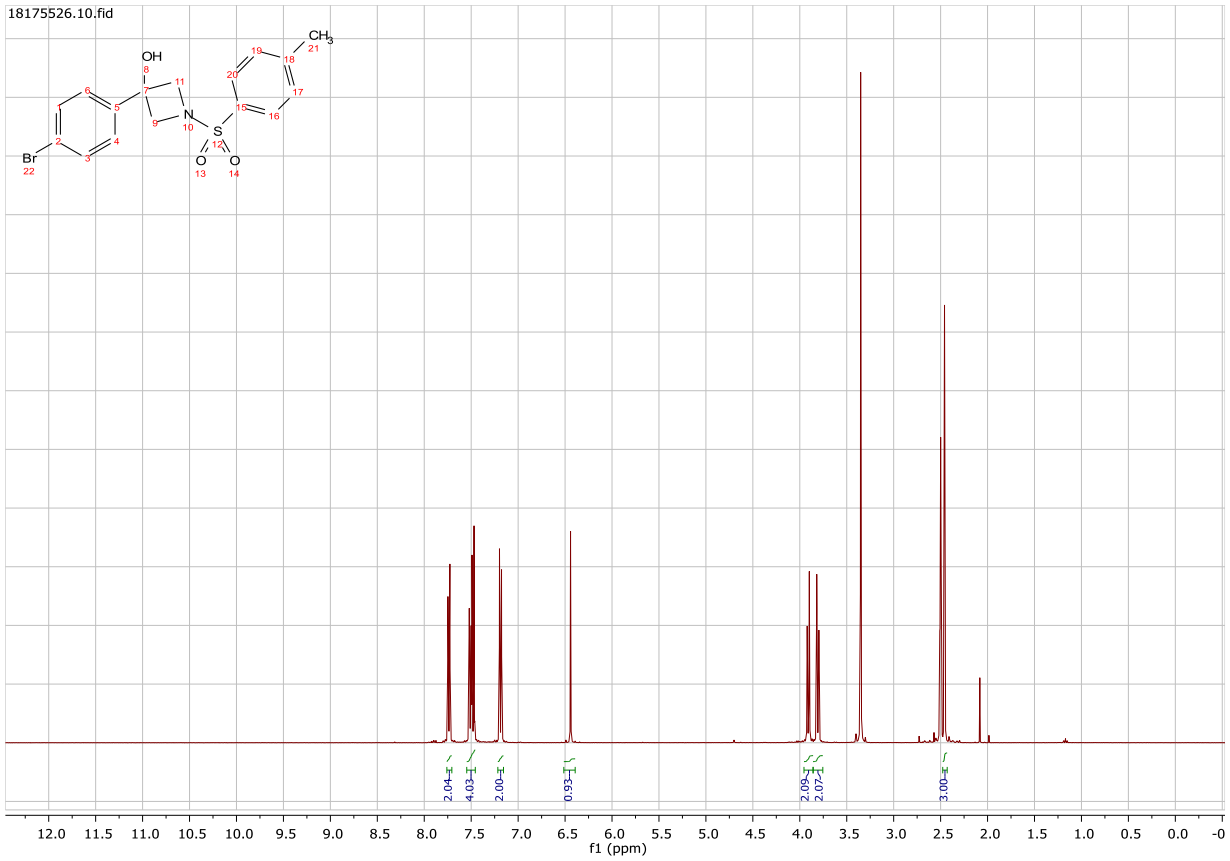
Compound 1-115 ^{1}H NMR (101 MHz, $CDCl_3$)



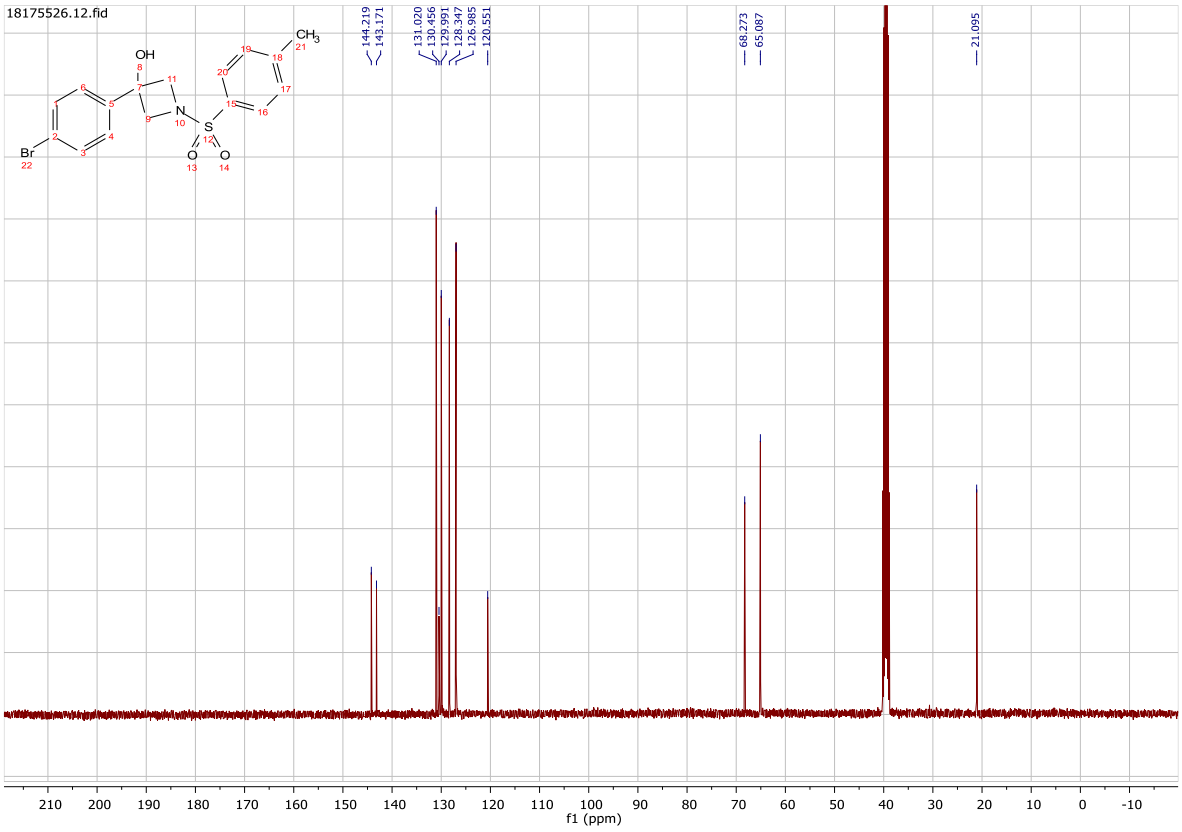
Compound 1-115a ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



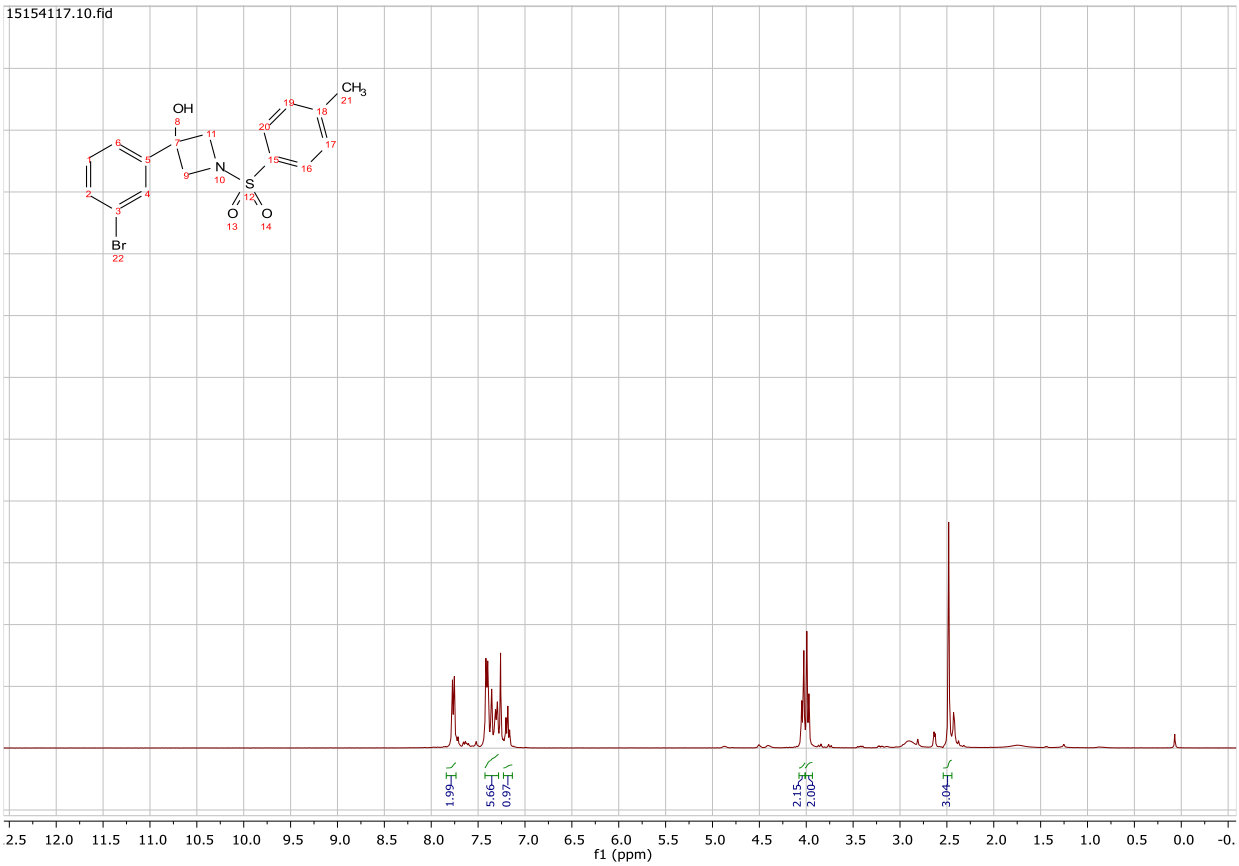
Compound 1-118 ^{1}H NMR (101 MHz, $CDCl_3$)



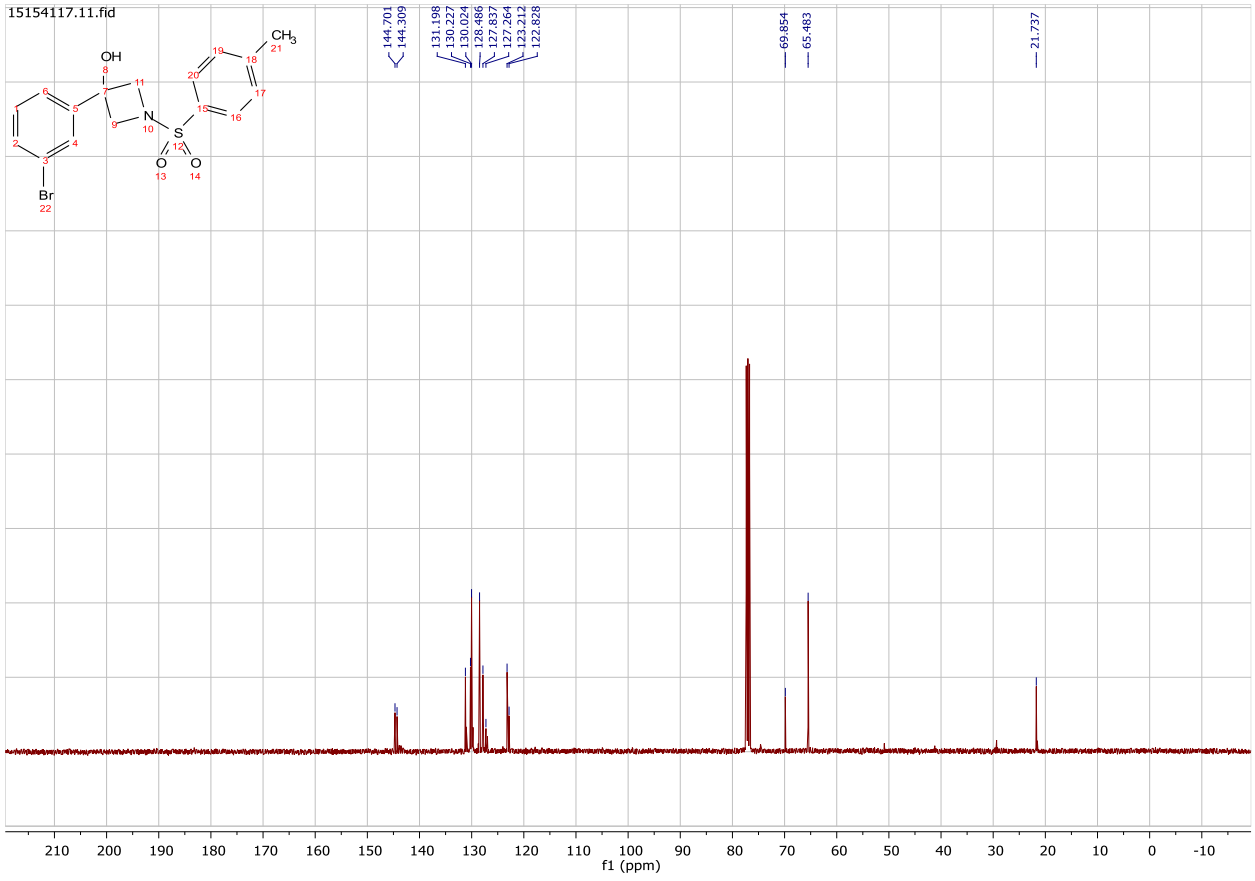
Compound 1-118 $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



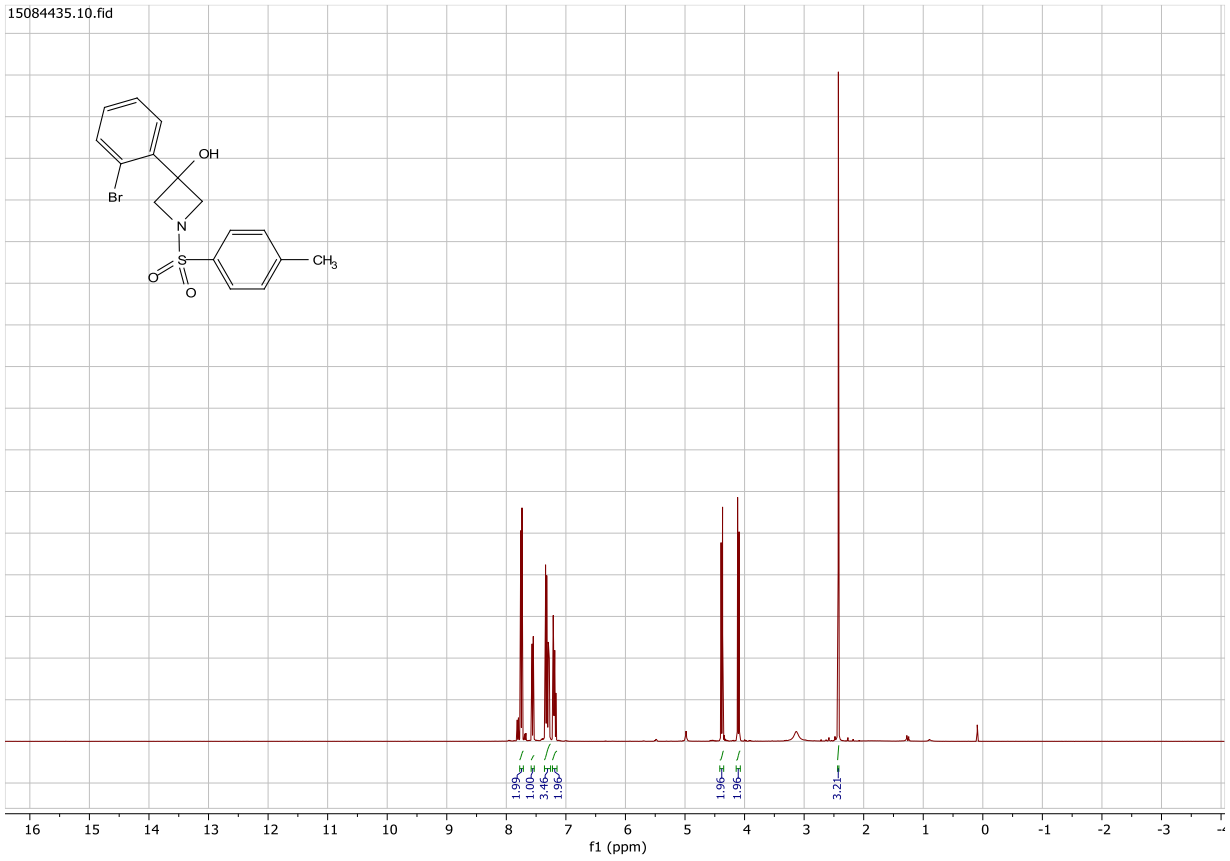
Compound 1-119 ^{1}H NMR (101 MHz, $CDCl_3$)



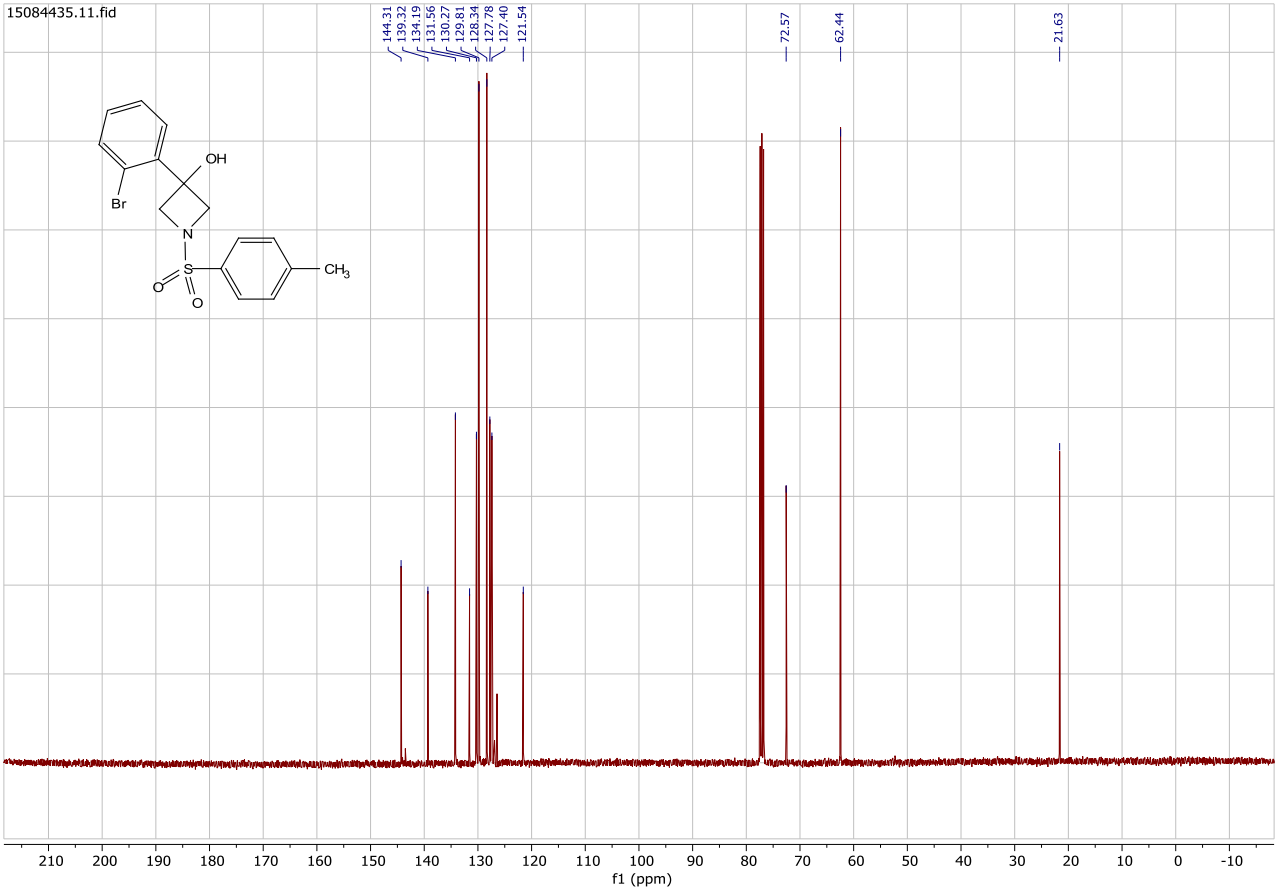
Compound 1-119 $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



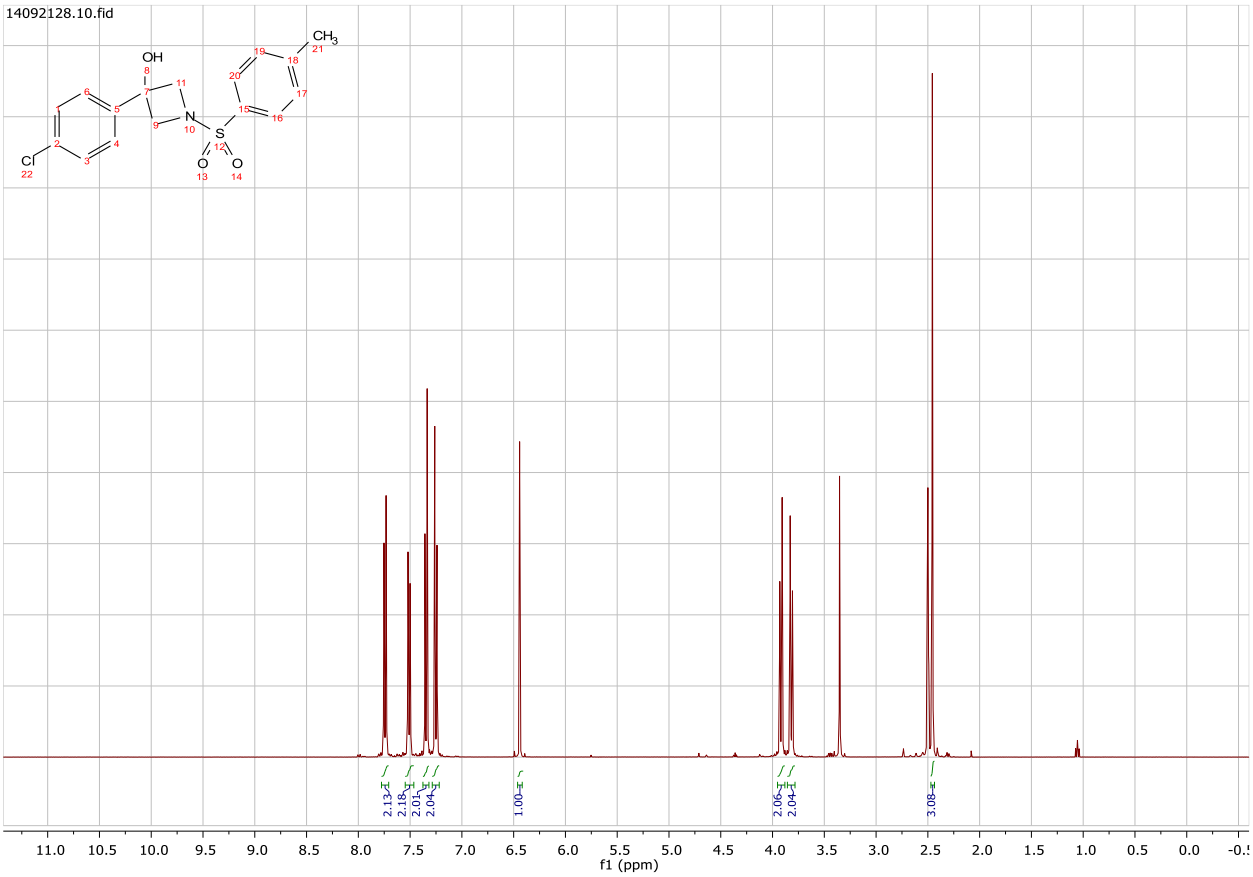
Compound 1-120 ^{1}H NMR (101 MHz, $CDCl_3$)



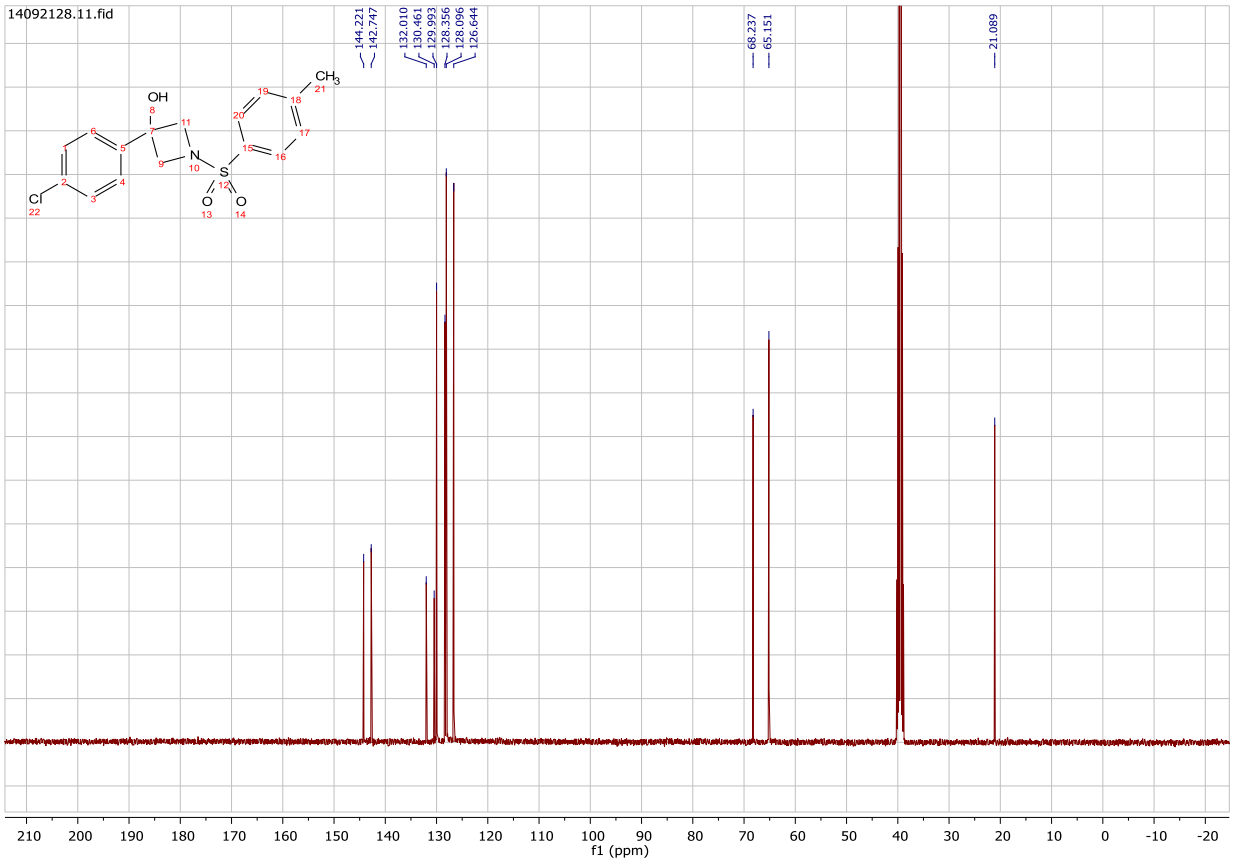
Compound 1-120 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



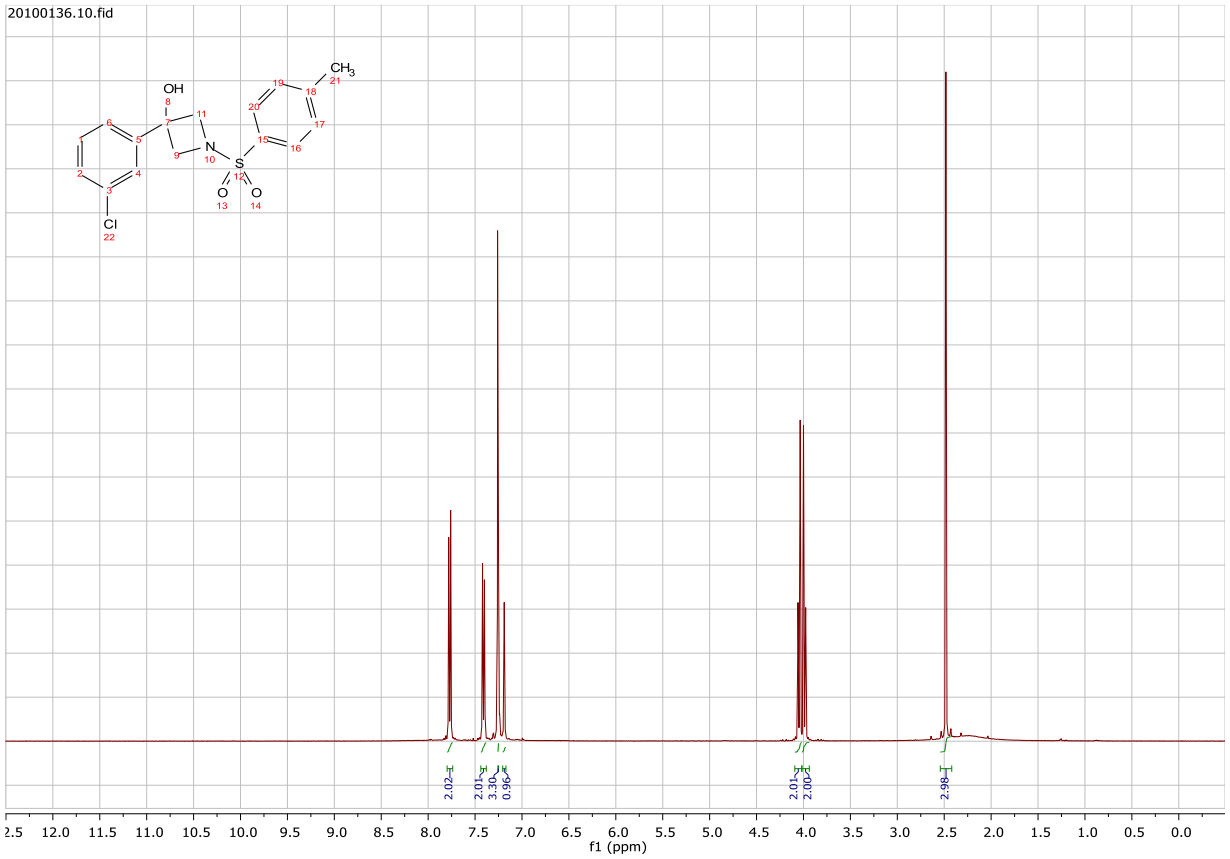
Compound 1-121 ^{1}H NMR (101 MHz, $CDCl_3$)



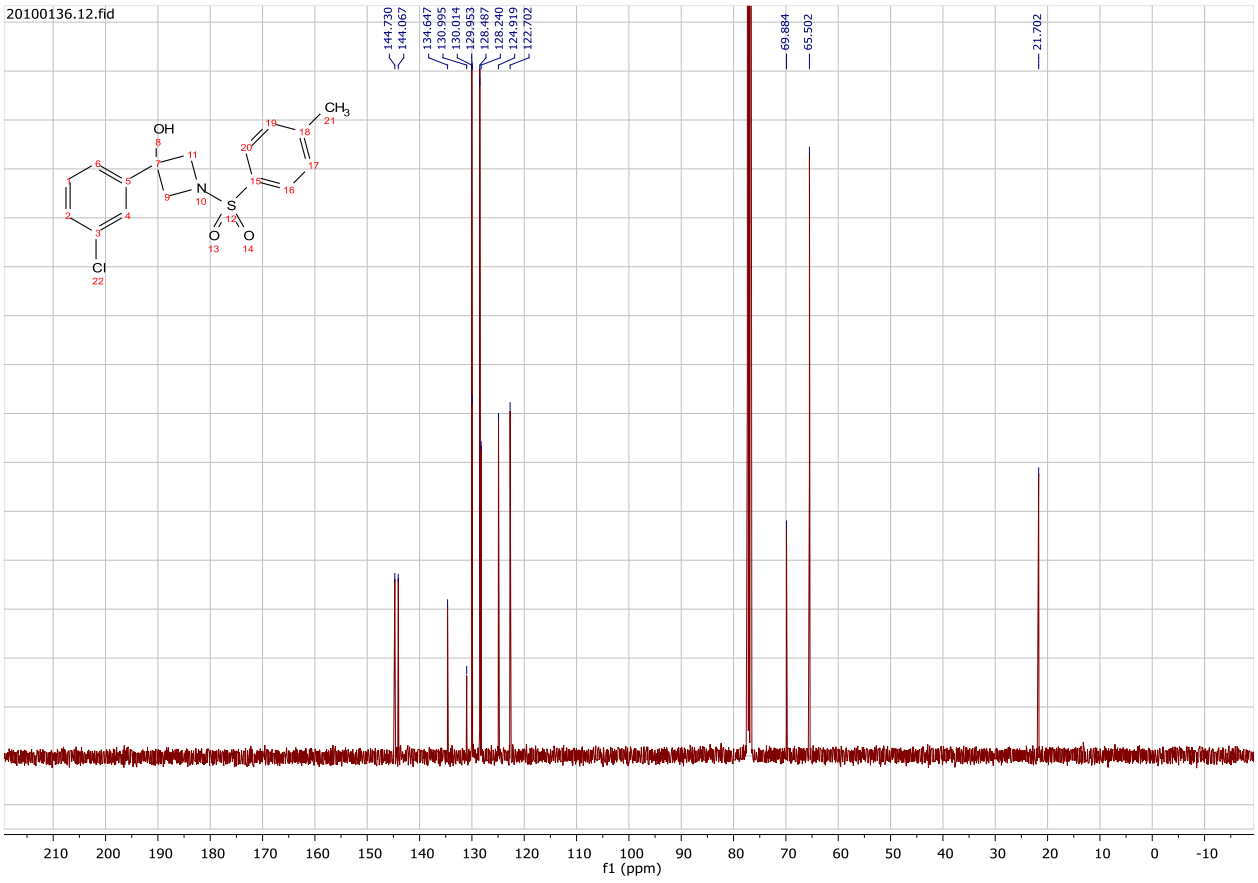
Compound 1-121 $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



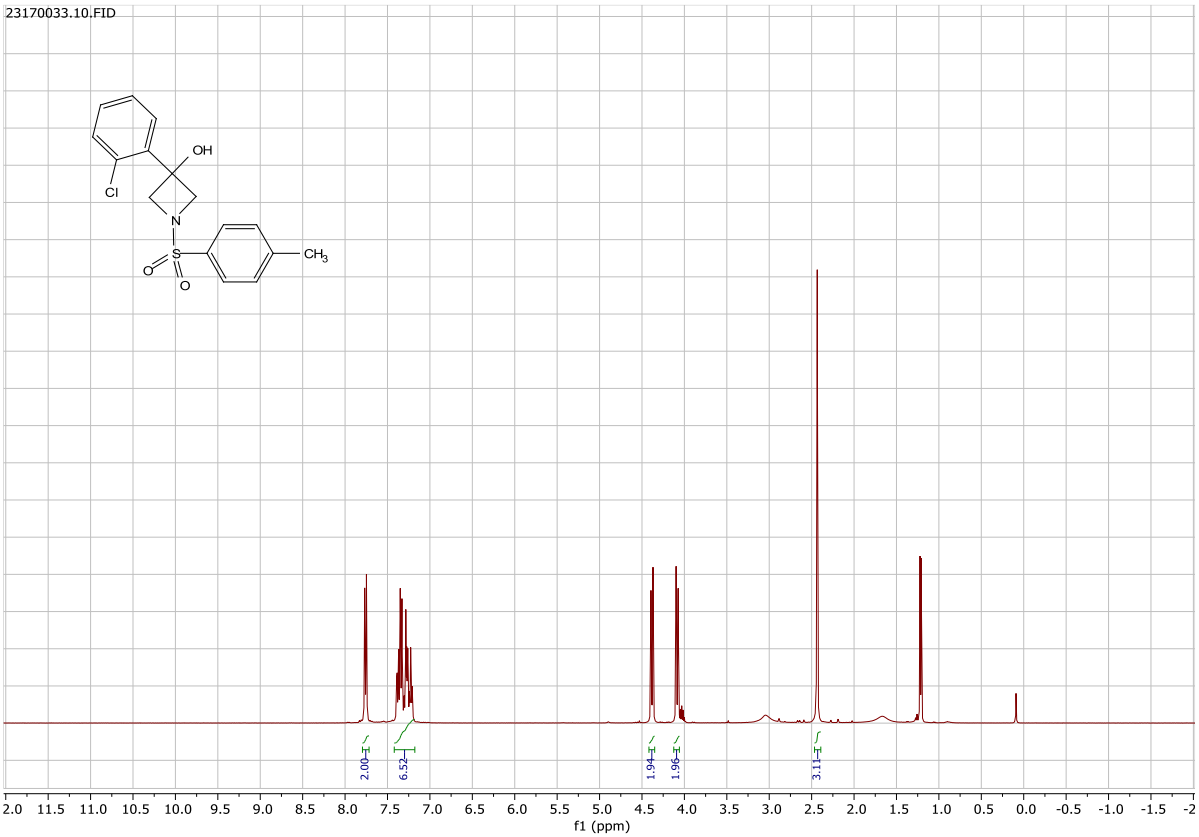
Compound 1-122 ^{1}H NMR (101 MHz, $CDCl_3$)



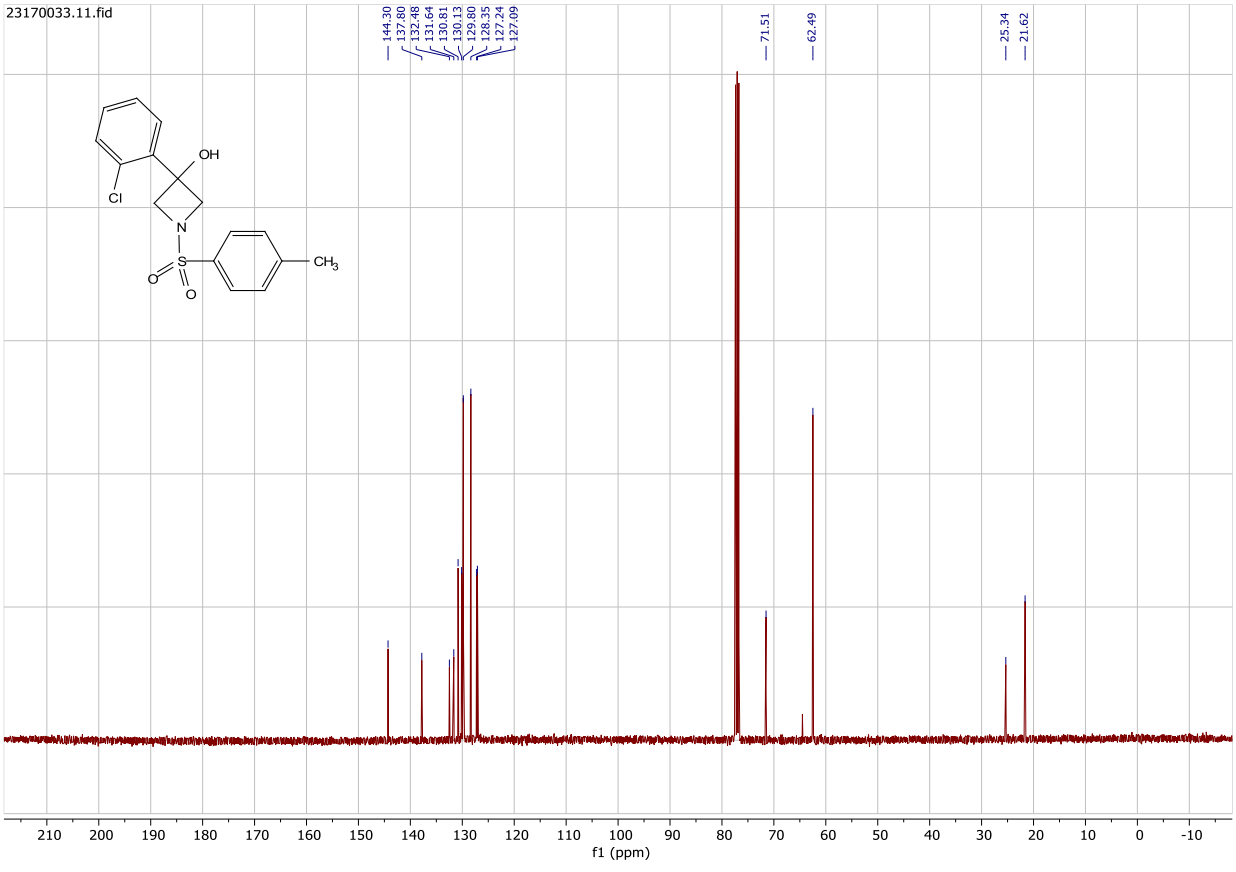
Compound 1-122 $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



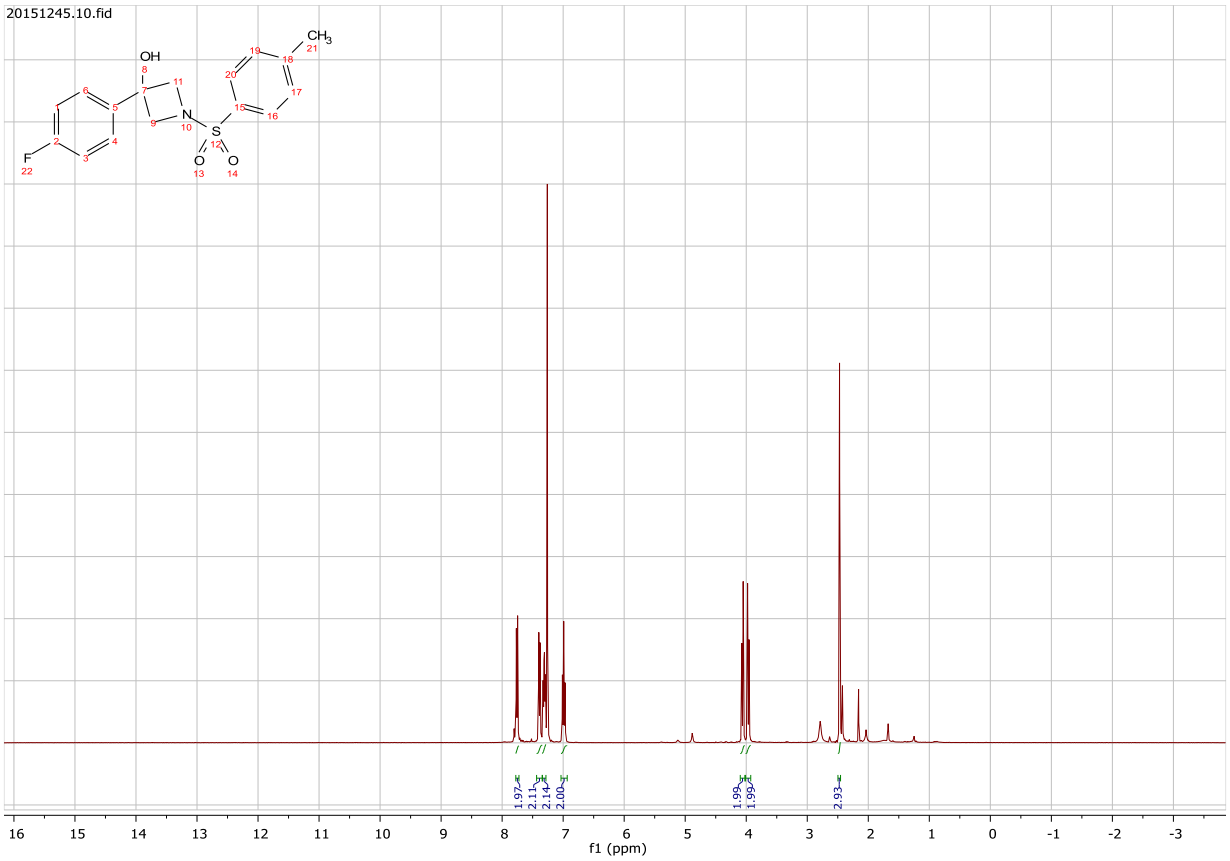
Compound 1-123 ^{1}H NMR (101 MHz, $CDCl_3$)



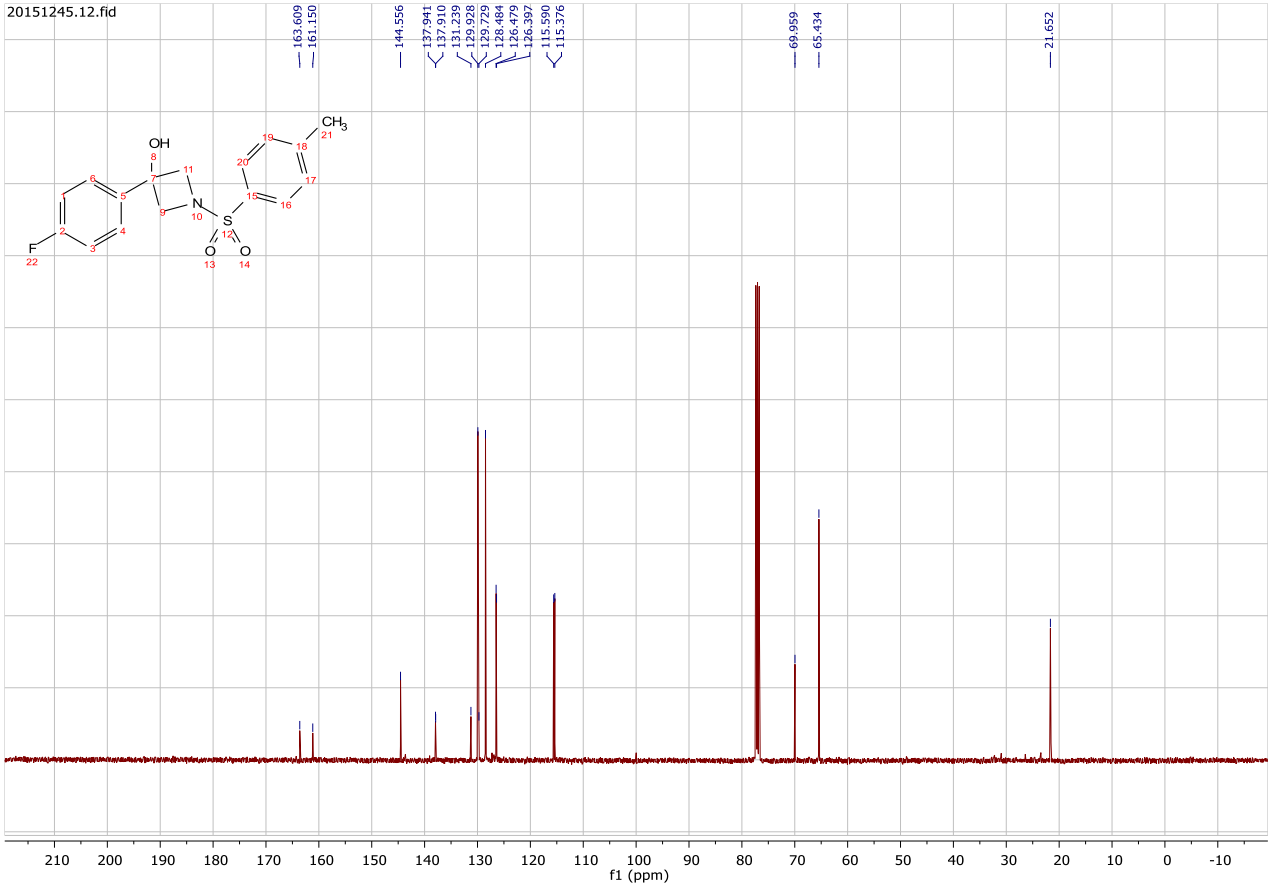
Compound 1-123 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



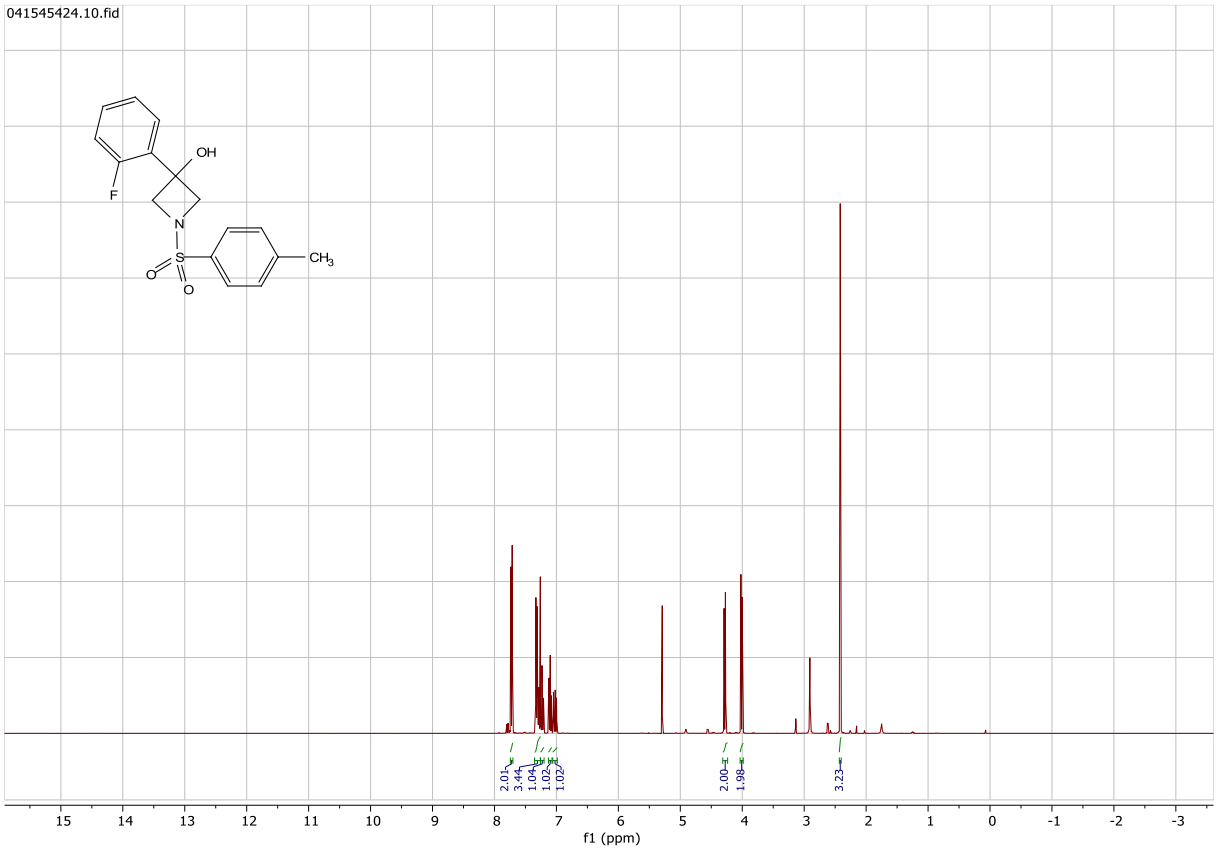
Compound 1-124 ^{1}H NMR (101 MHz, $CDCl_3$)



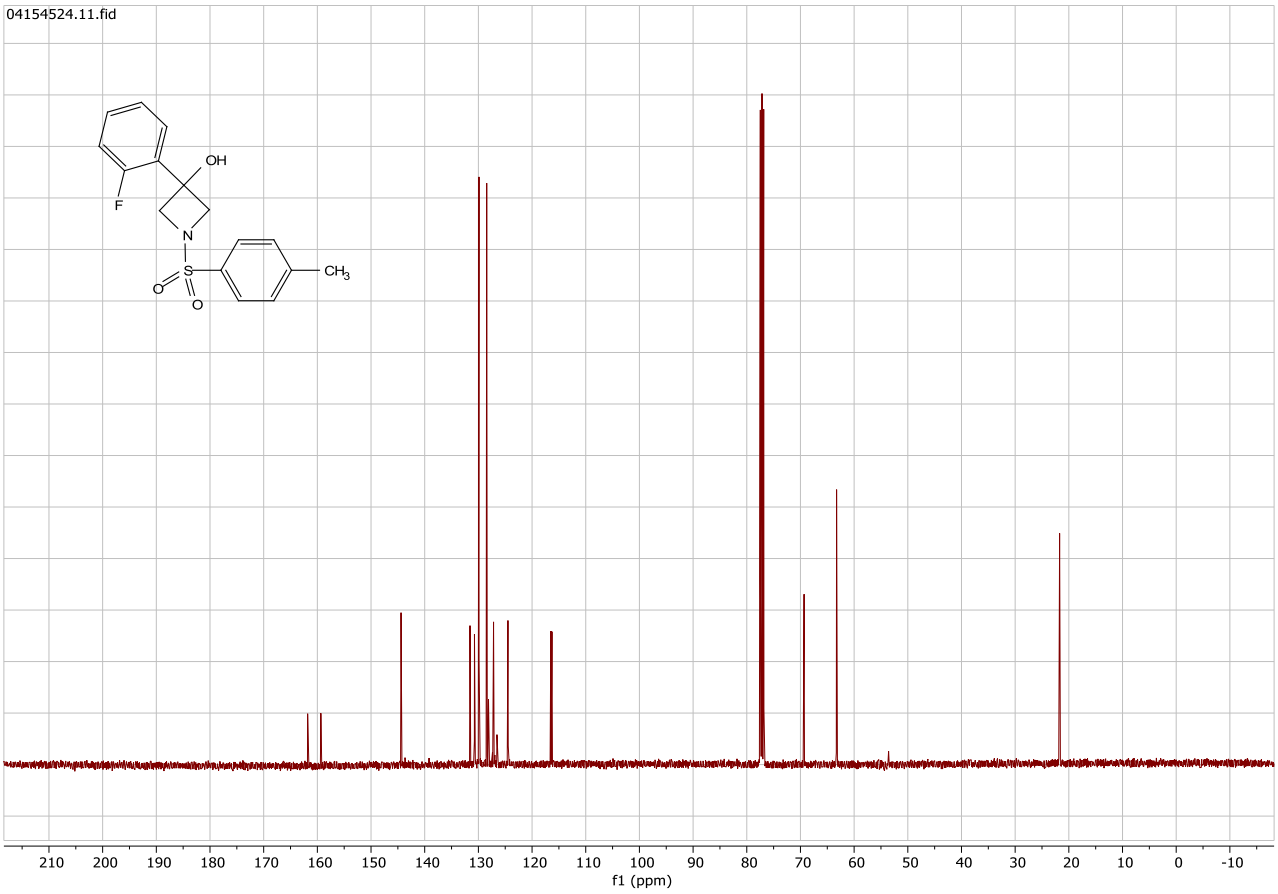
Compound 1-124 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



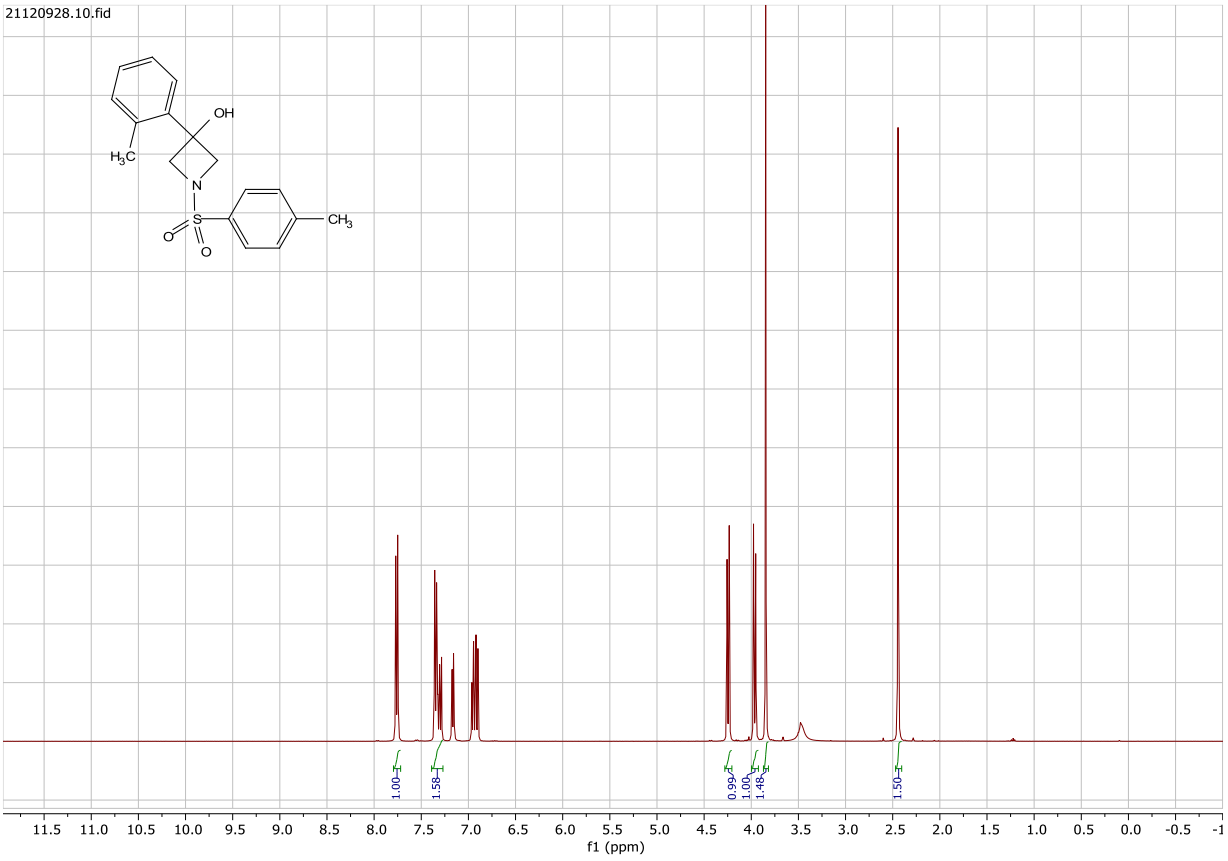
Compound 1-125 ^{1}H NMR (101 MHz, $CDCl_3$)



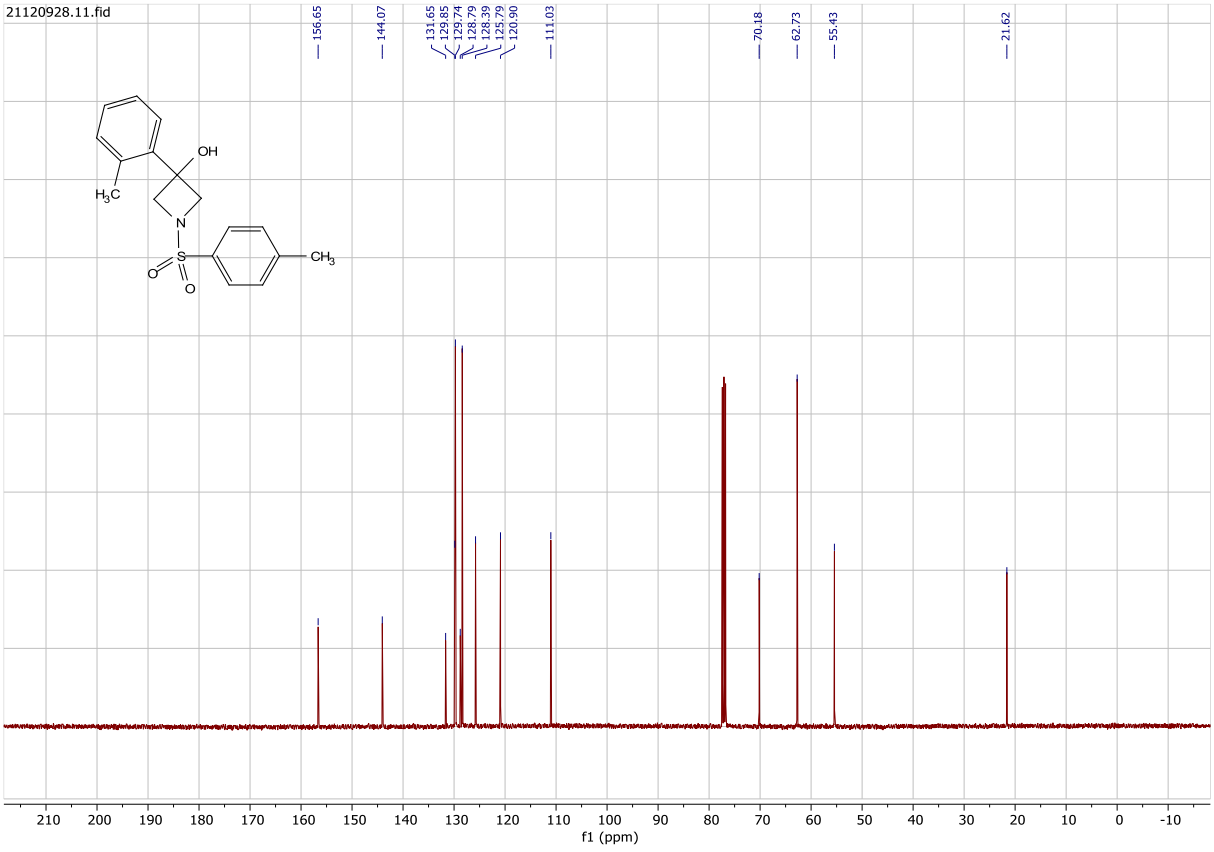
Compound 1-125 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



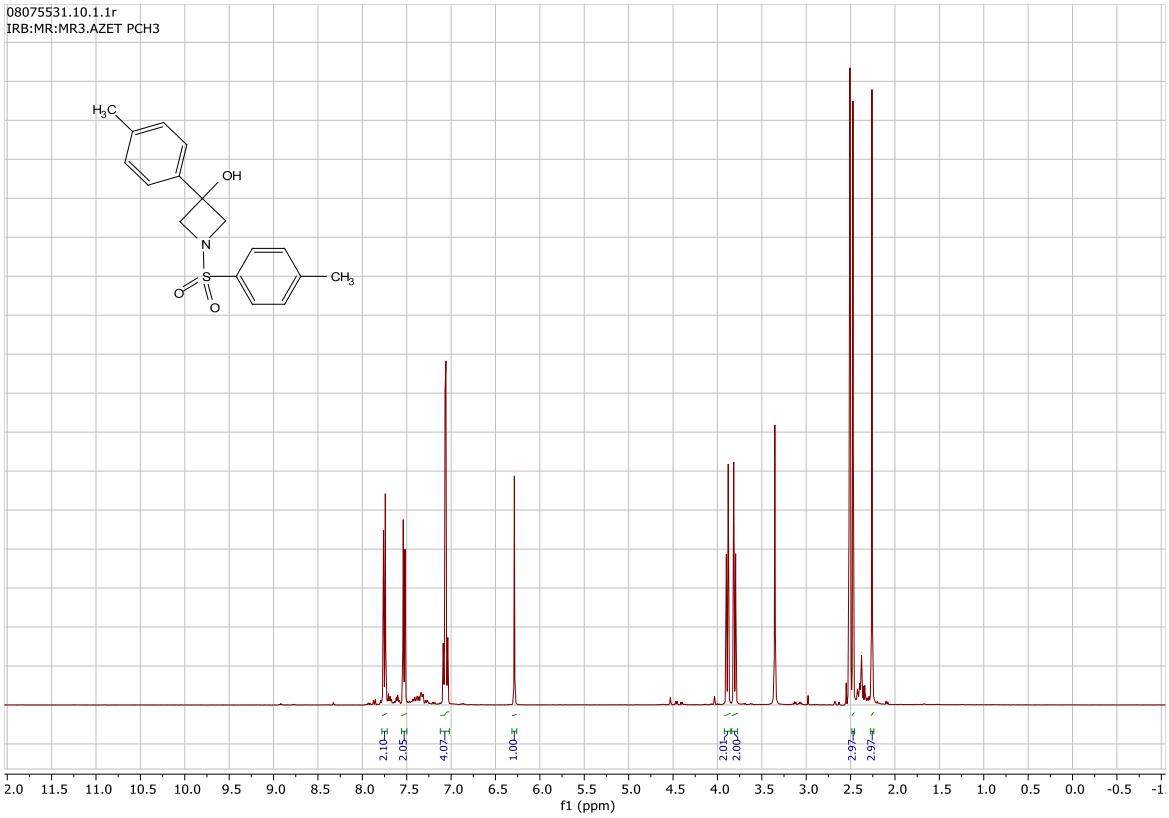
Compound 1-126 ^{1}H NMR (101 MHz, $CDCl_3$)



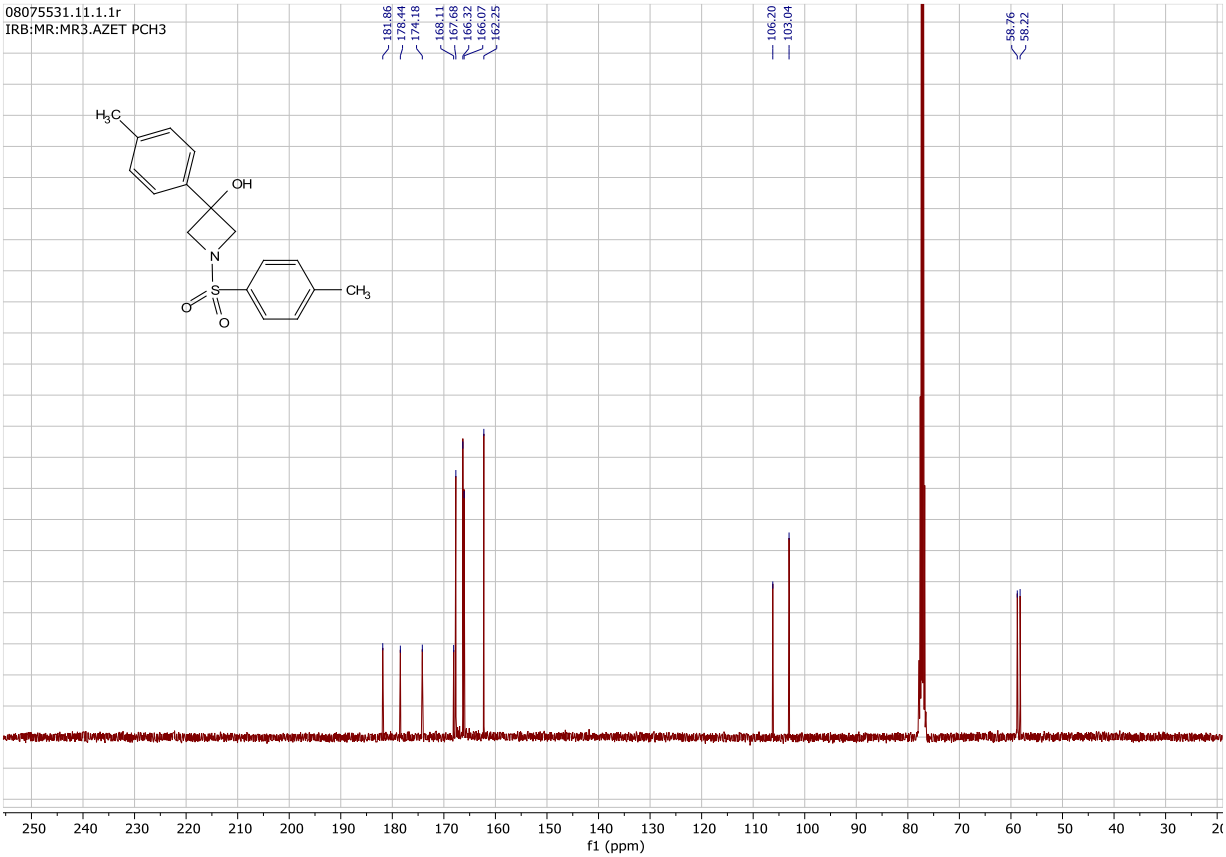
Compound 1-126 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



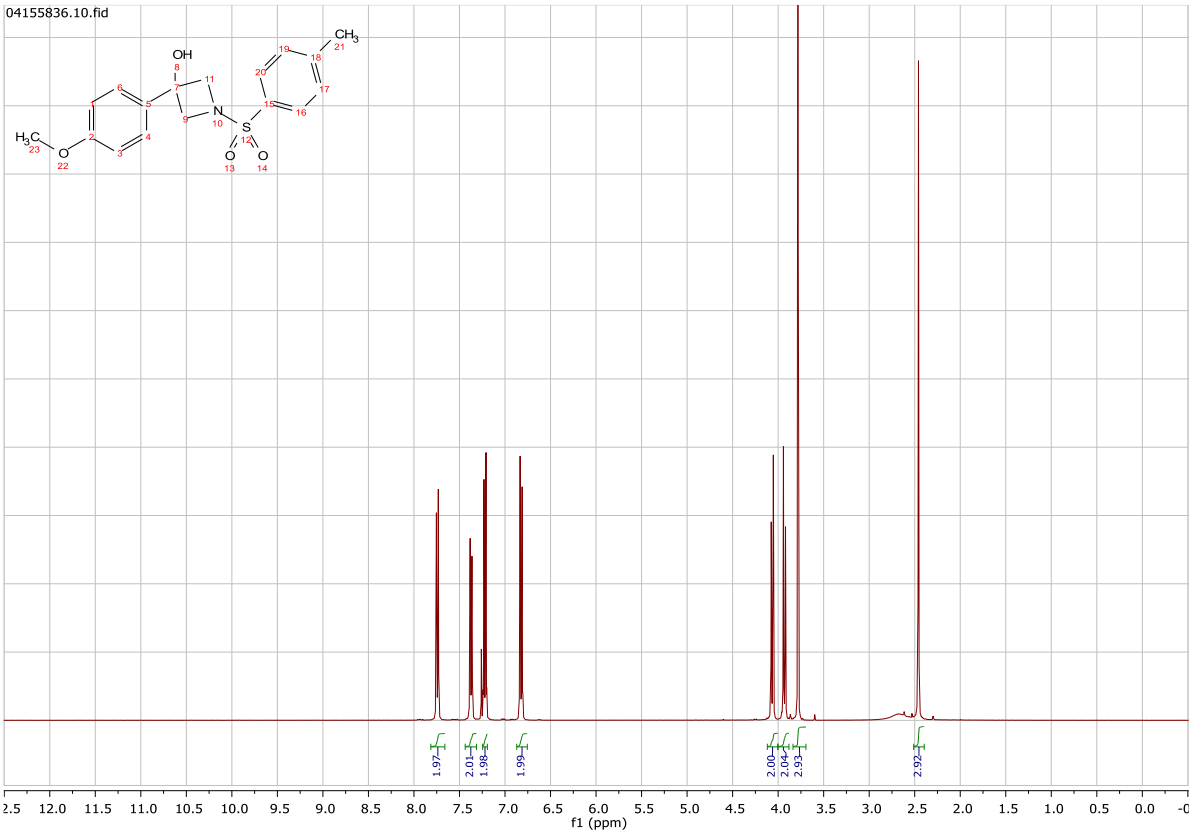
Compound 1-127 ^{1}H NMR (101 MHz, $CDCl_3$)



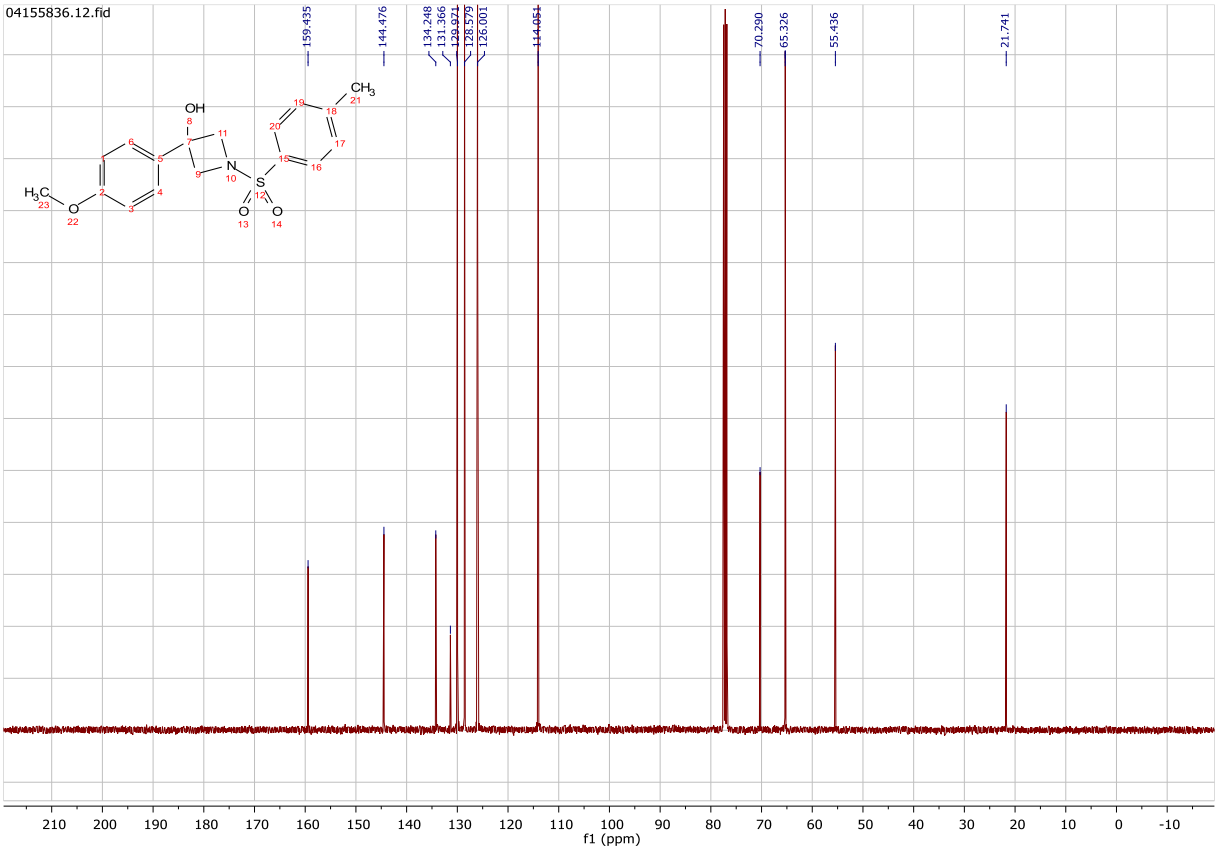
Compound 1-127 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



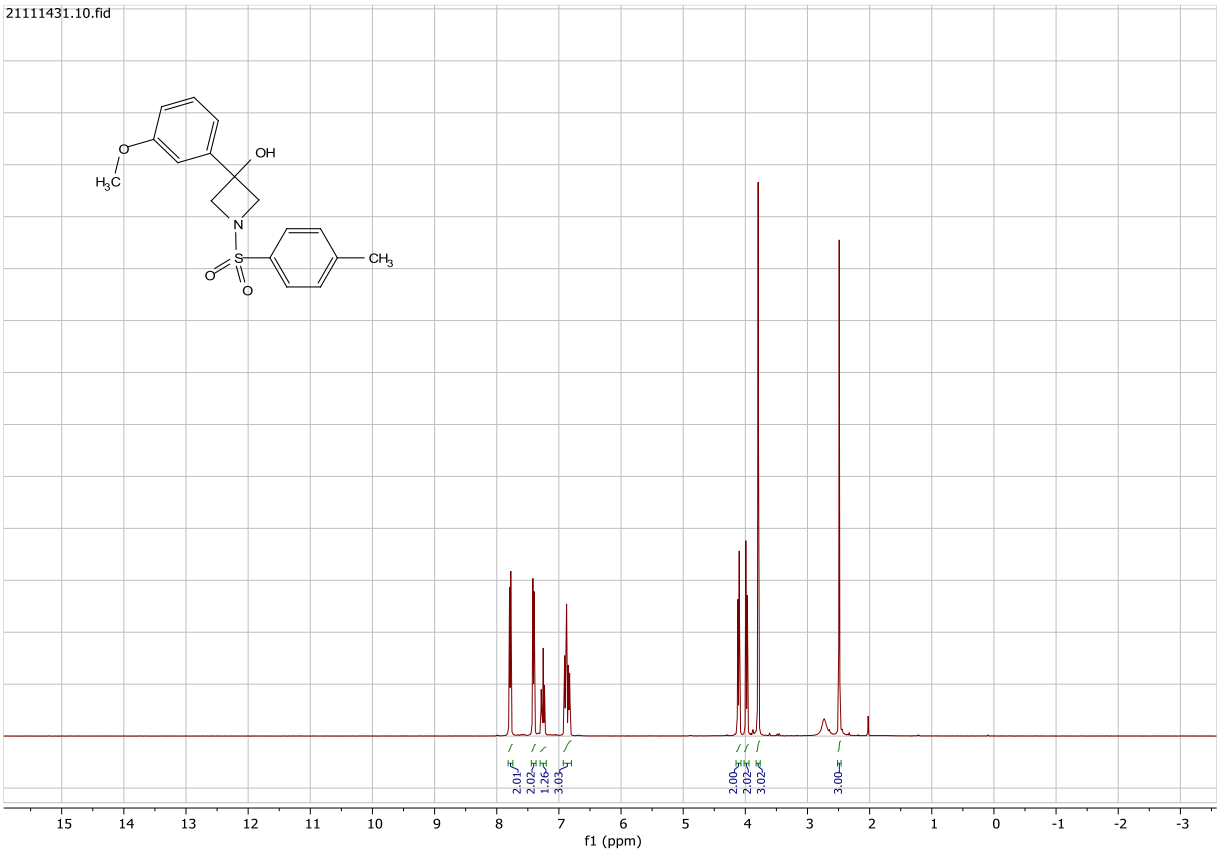
Compound 1-128 ^{1}H NMR (101 MHz, $CDCl_3$)



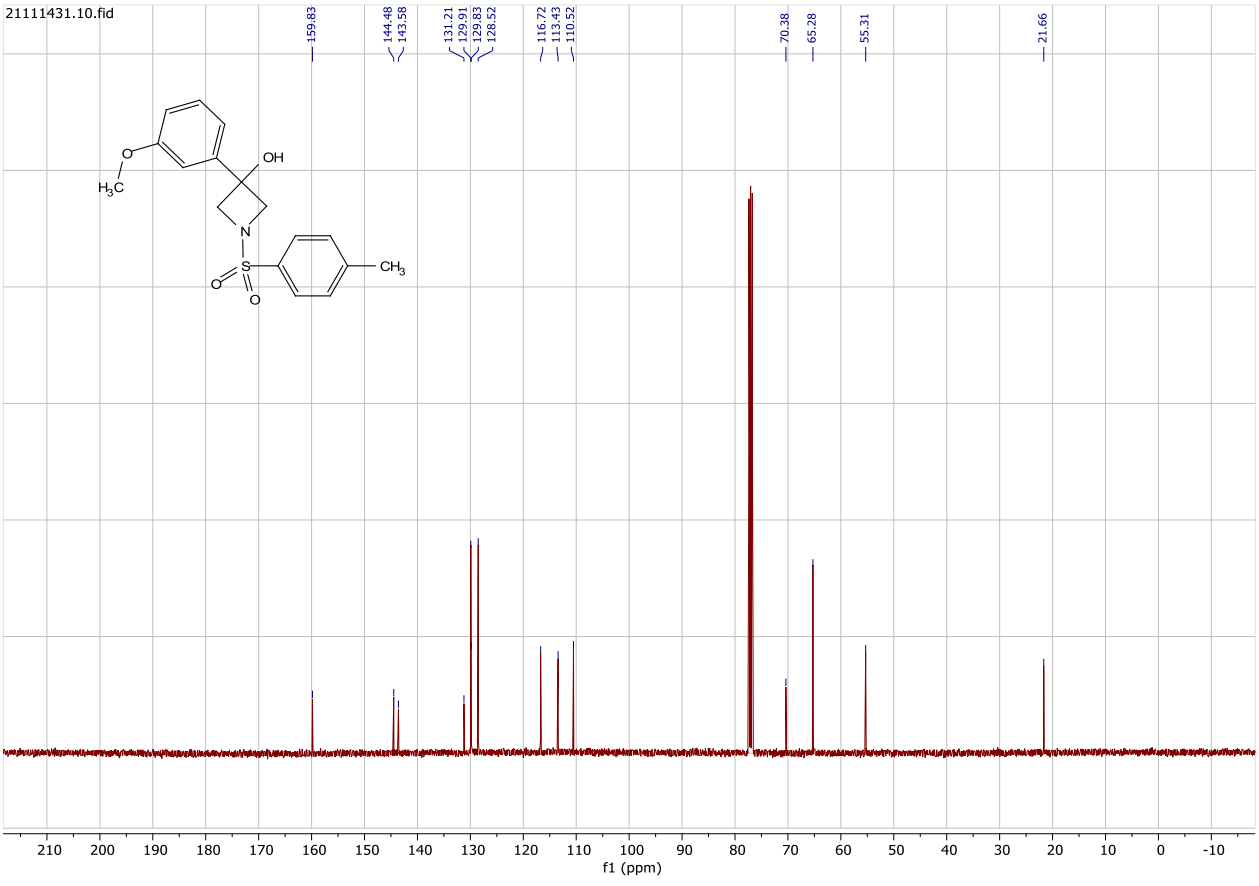
Compound 1-128 $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



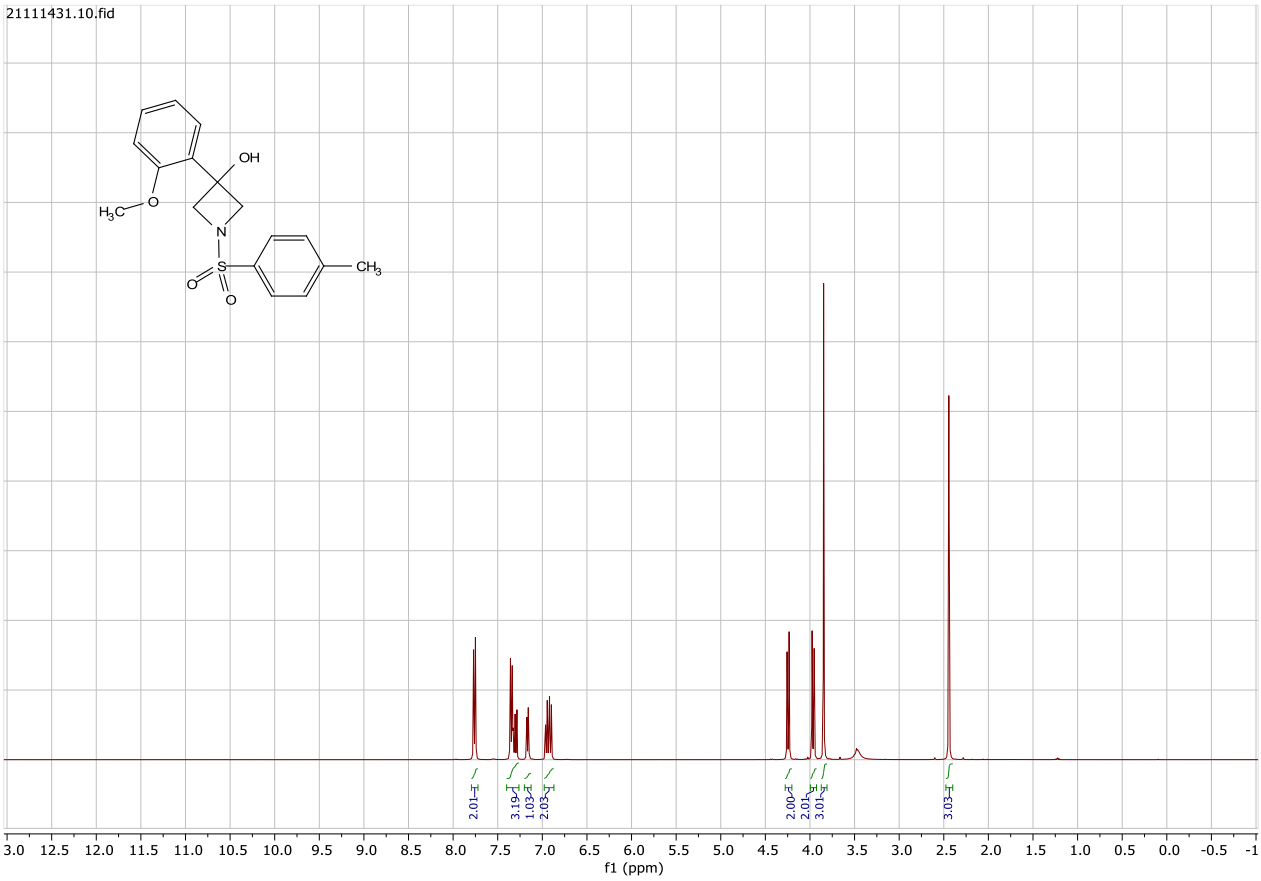
Compound 1-129 ^{1}H NMR (101 MHz, $CDCl_3$)



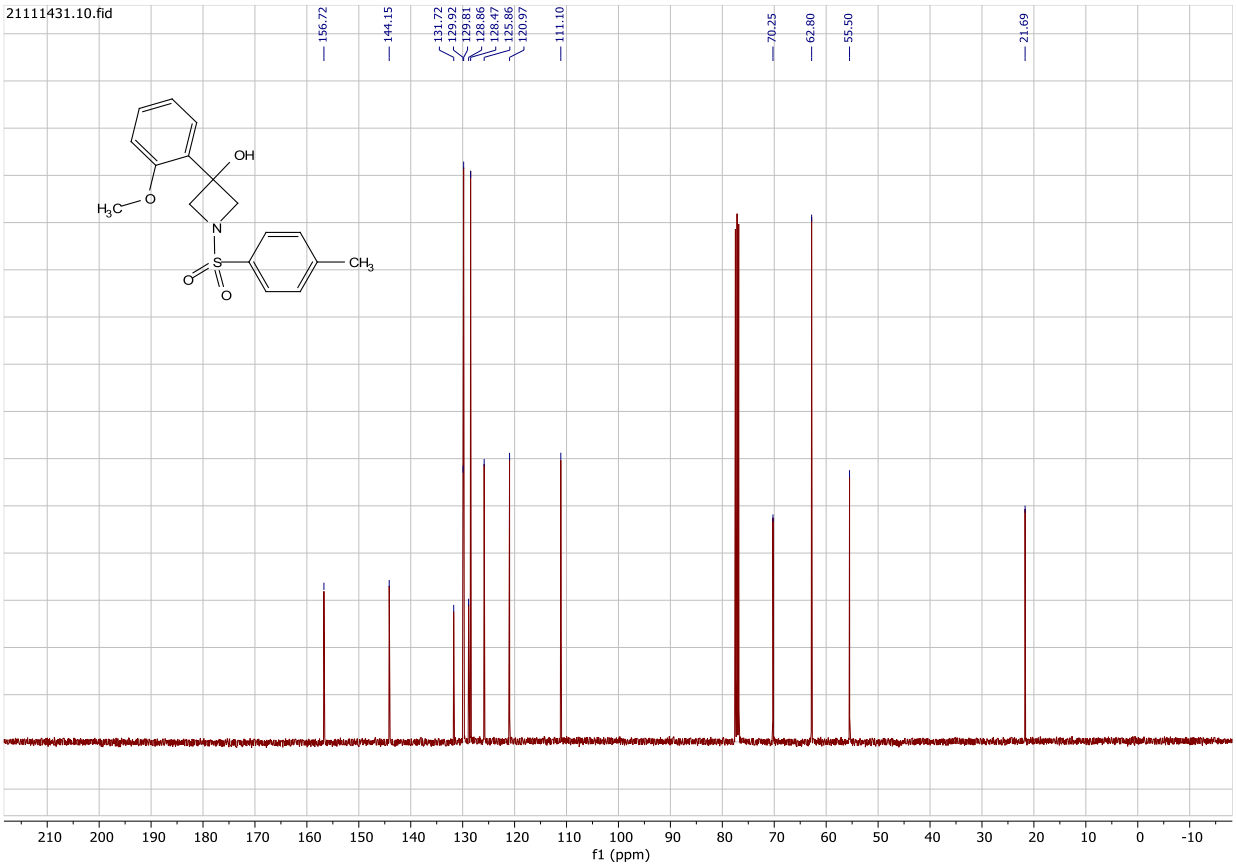
Compound 1-129 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



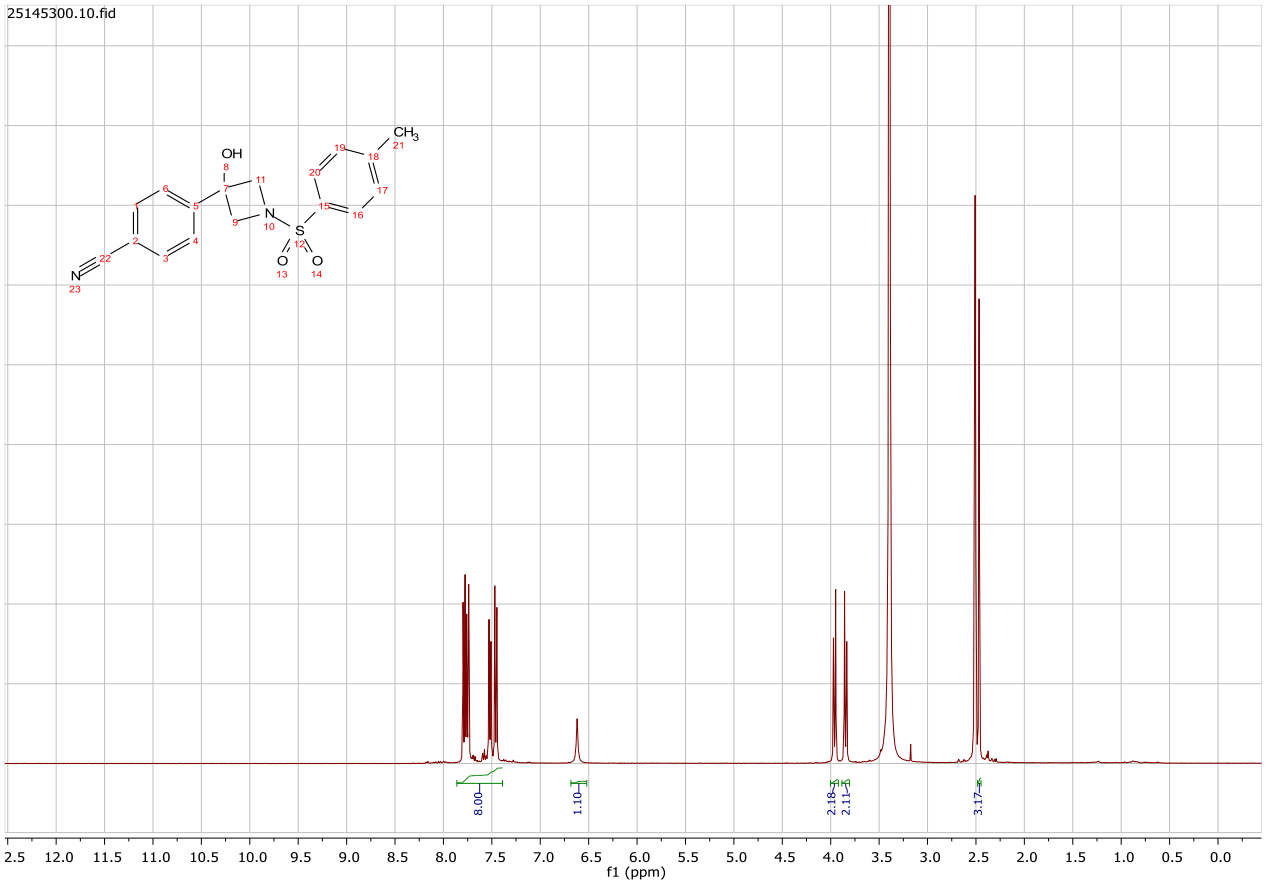
Compound 1-130 ^{1}H NMR (101 MHz, $CDCl_3$)



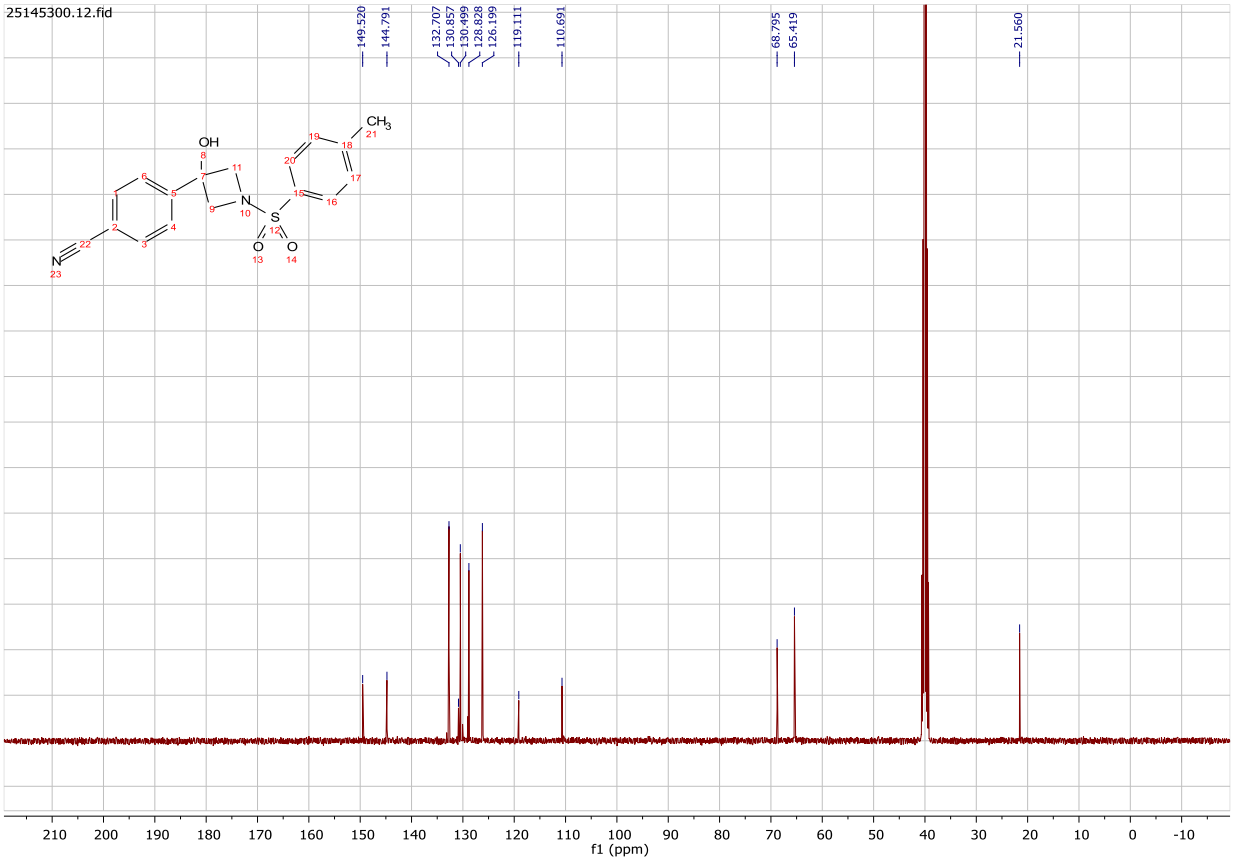
Compound 1-130 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



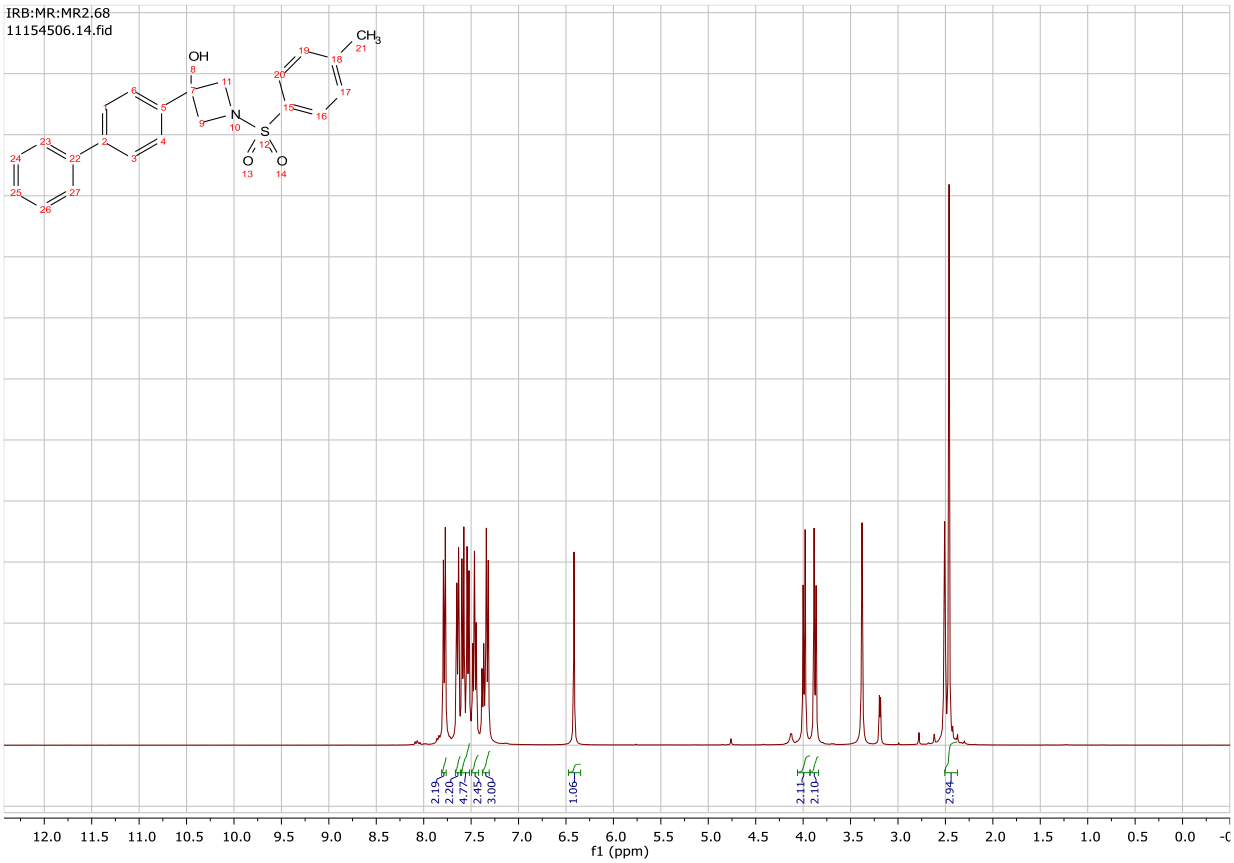
Compound 1-131 ^{1}H NMR (101 MHz, $CDCl_3$)



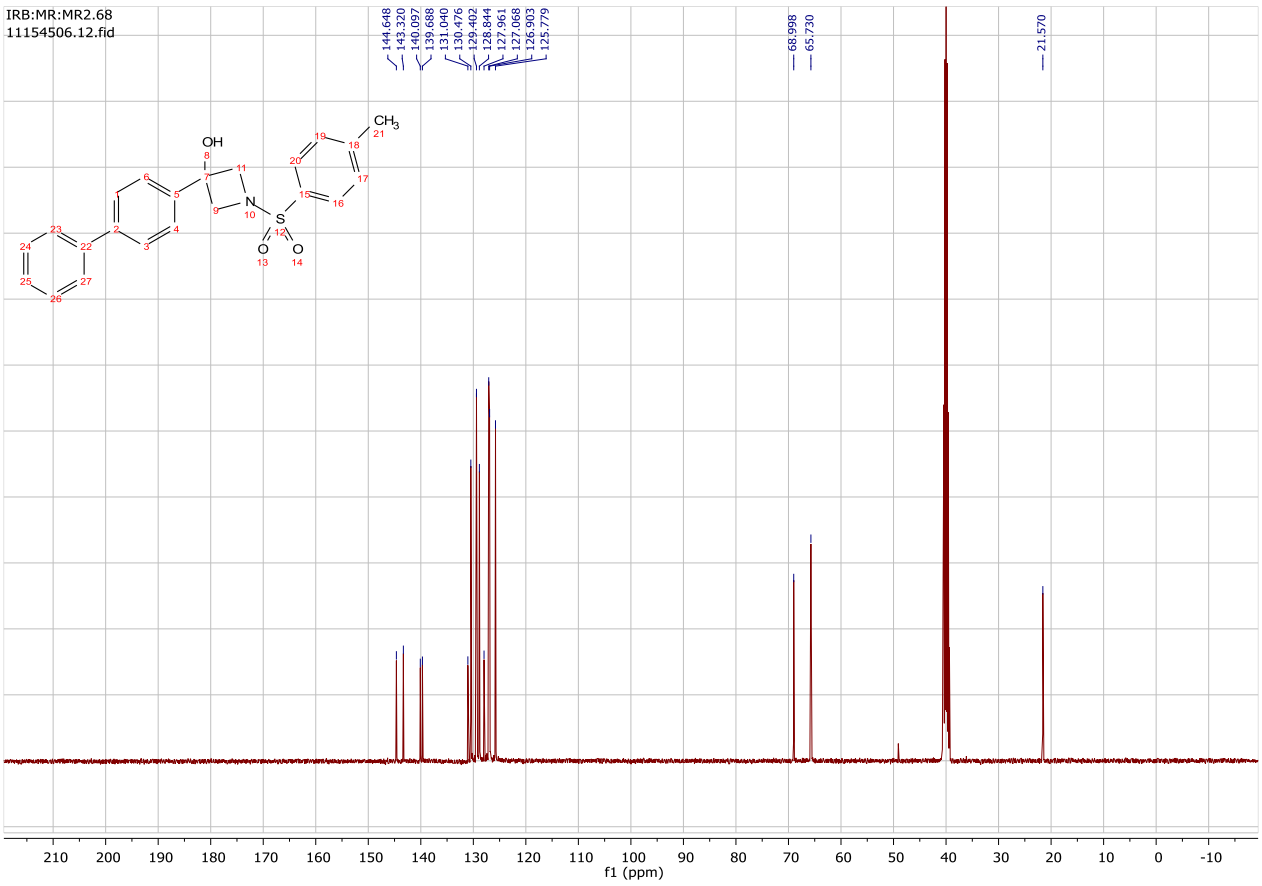
Compound 1-131 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



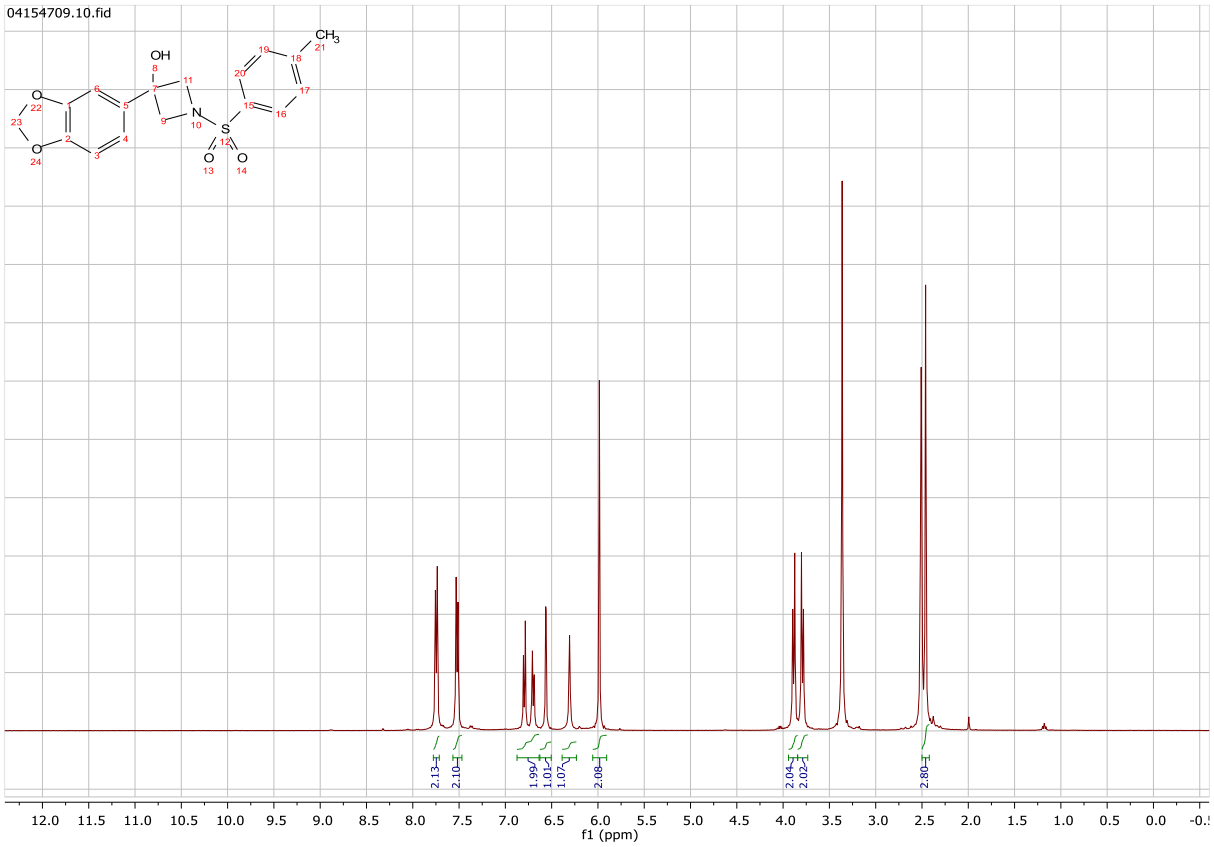
Compound 1-132 ^{1}H NMR (101 MHz, $CDCl_3$)



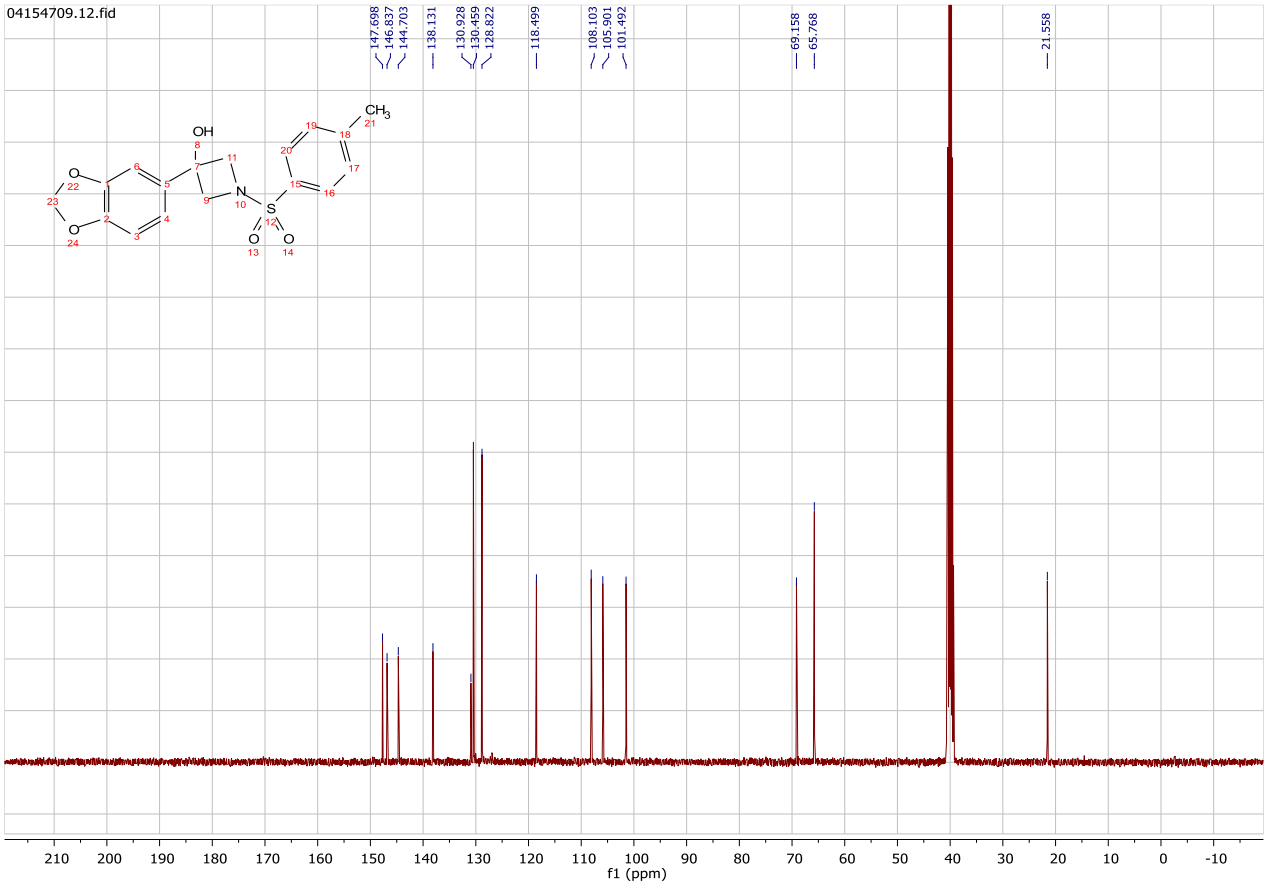
Compound 1-132 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



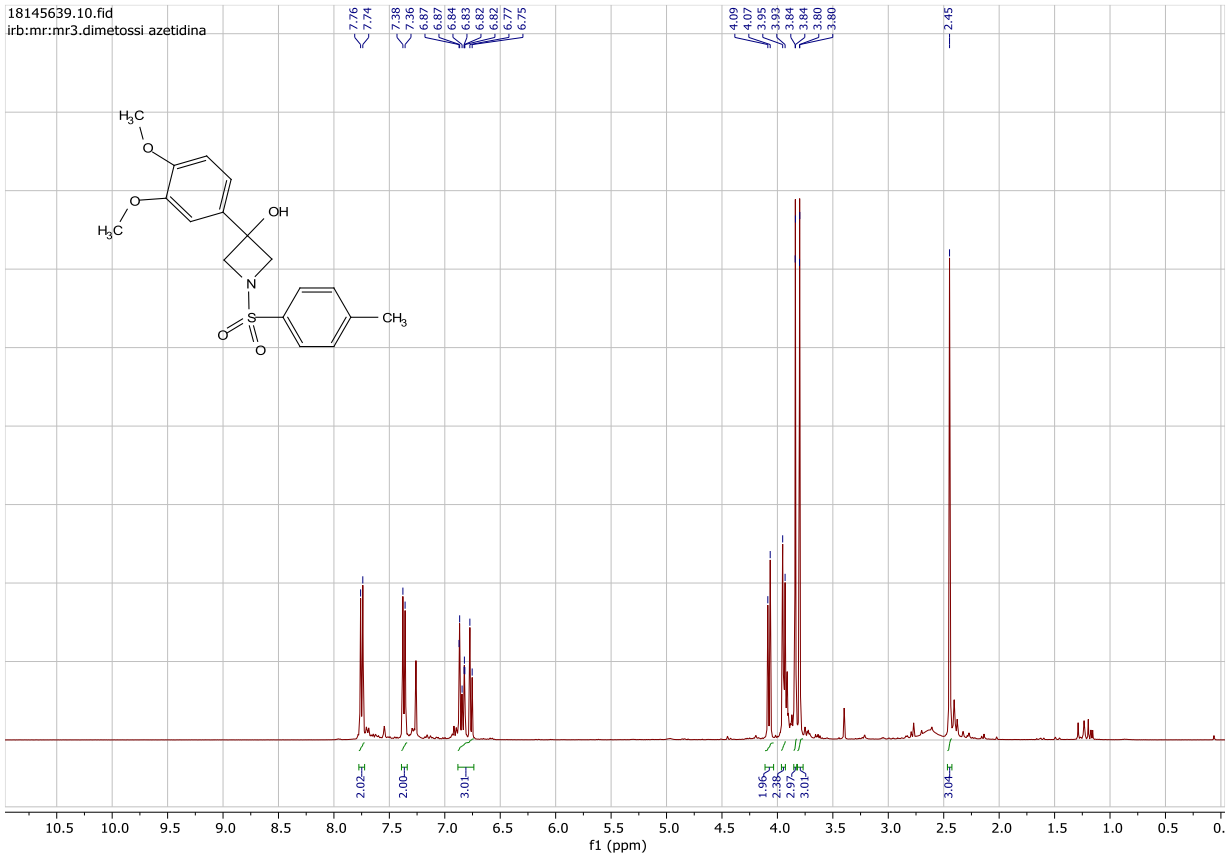
Compound 1-133 ^{1}H NMR (101 MHz, $CDCl_3$)



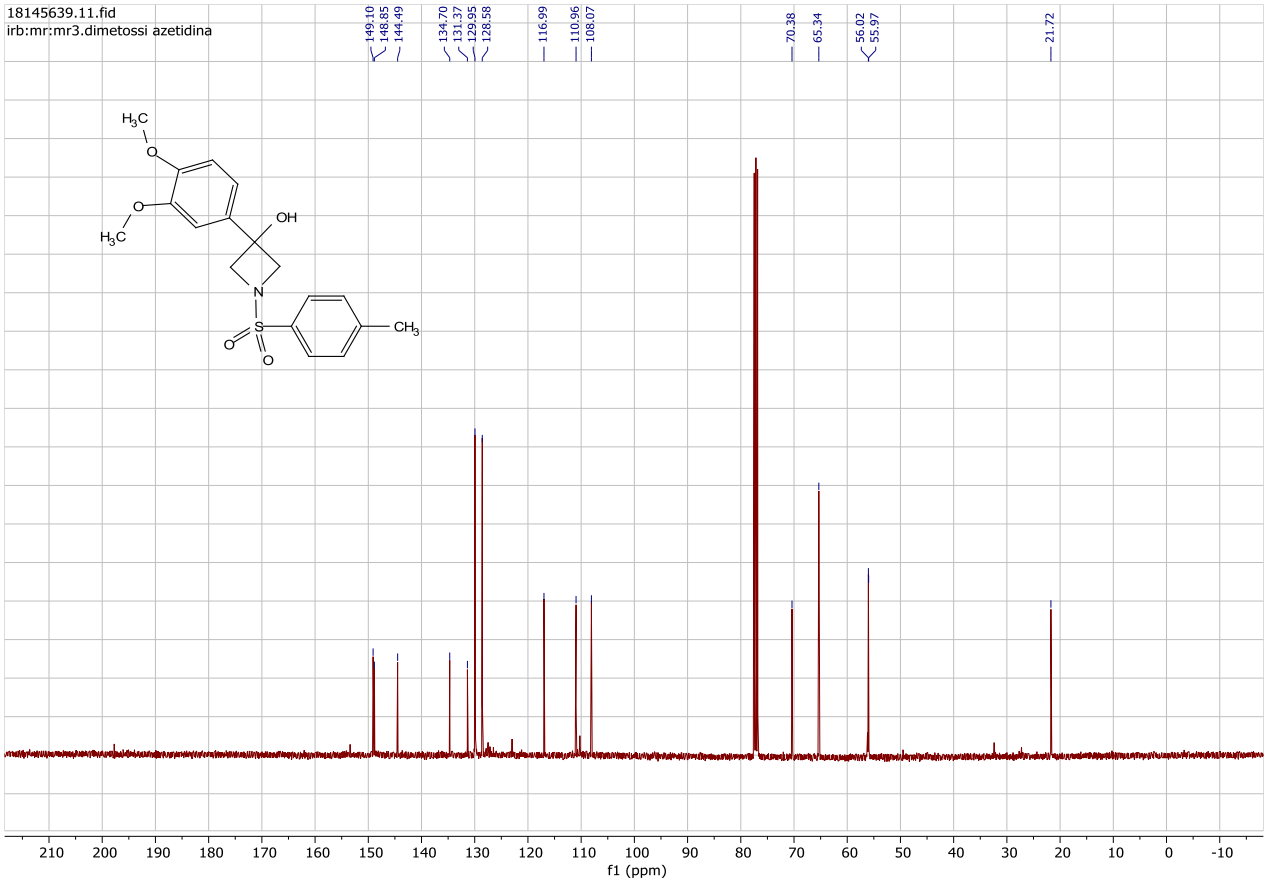
Compound 1-133 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



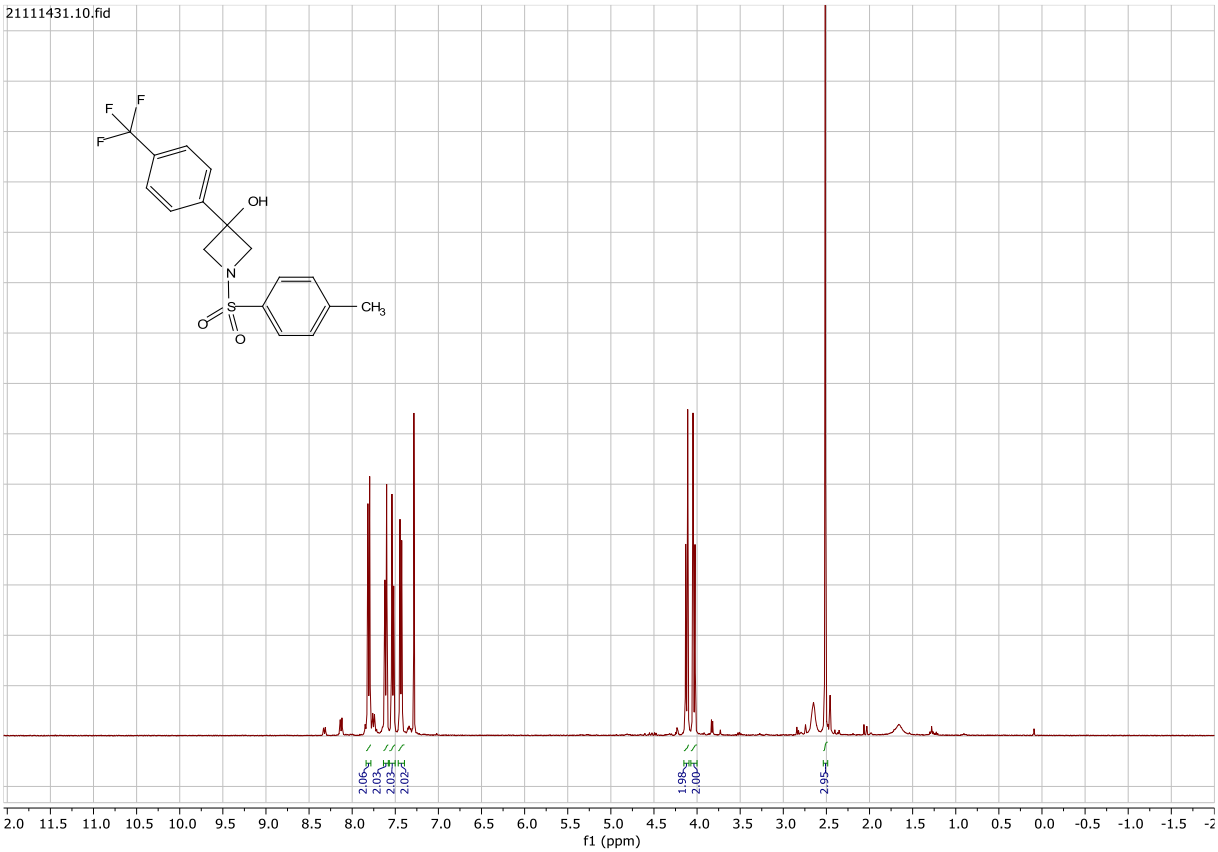
Compound 1-134 ^{1}H NMR (101 MHz, $CDCl_3$)



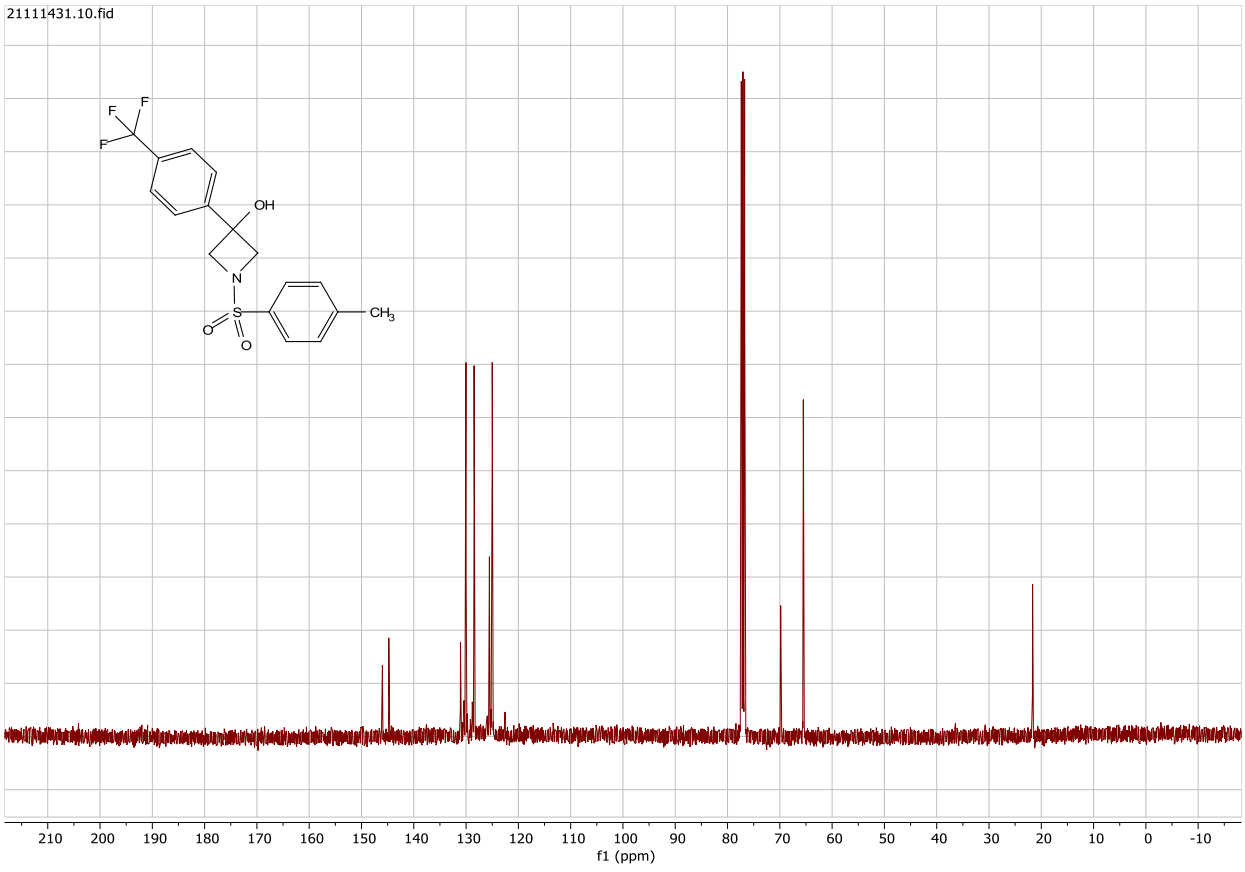
Compound 1-134 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



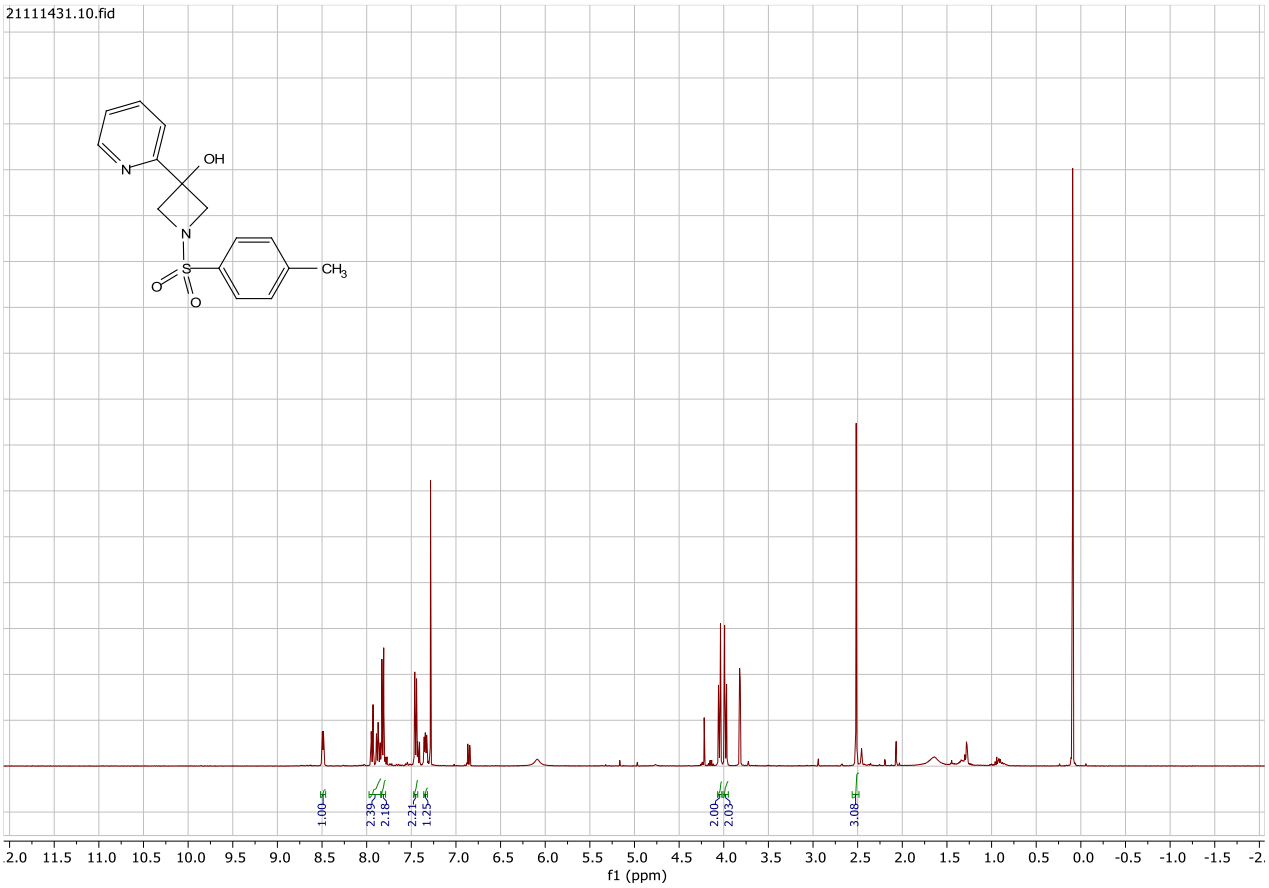
Compound 1-135 ^{1}H NMR (101 MHz, $CDCl_3$)



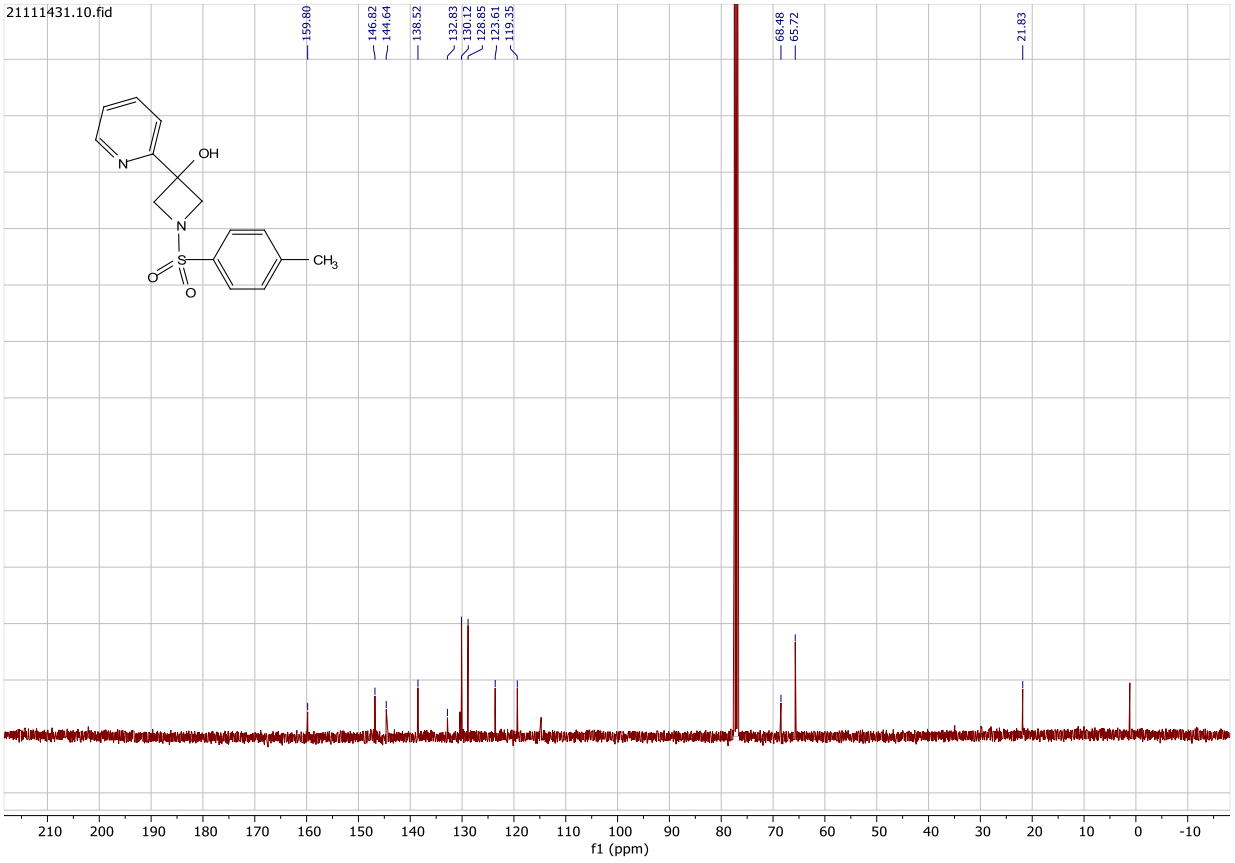
Compound 1-135 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



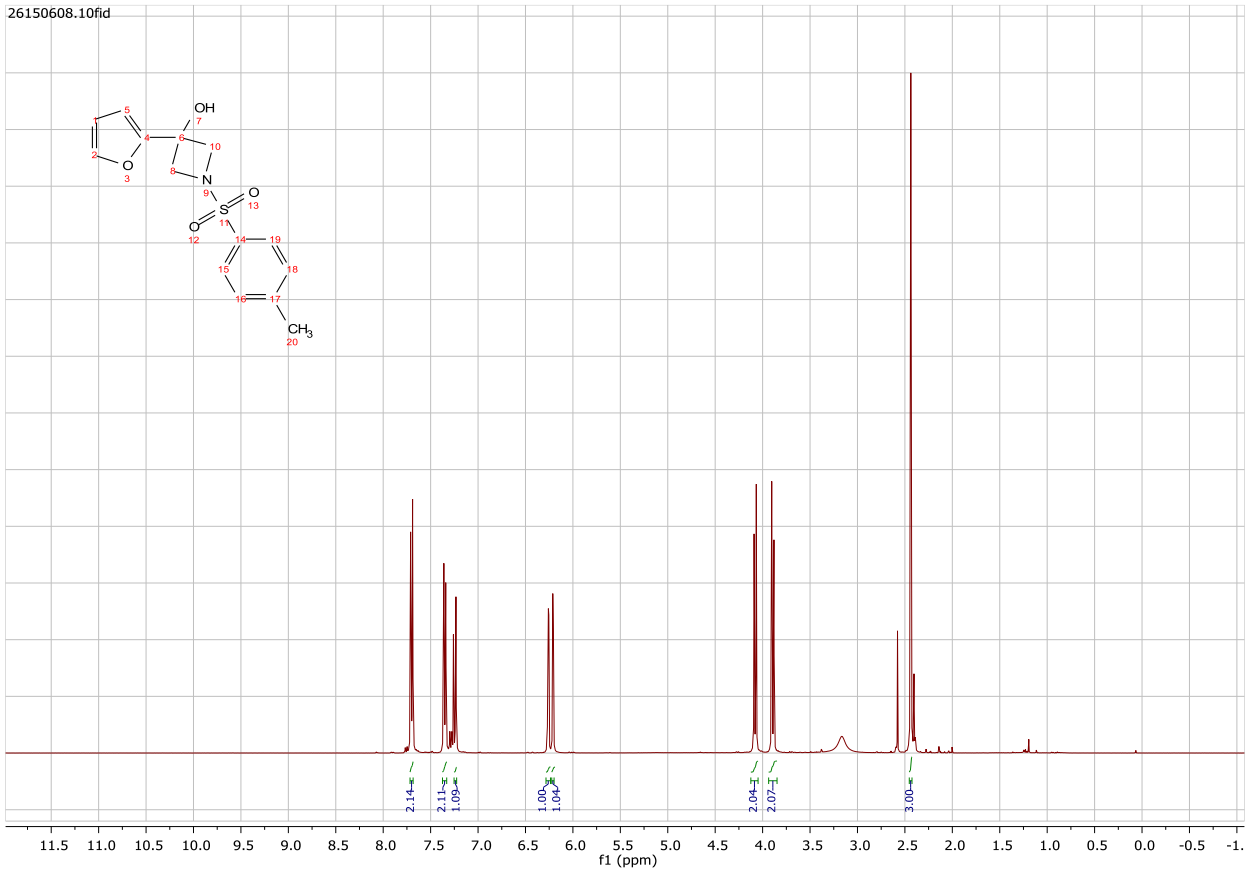
Compound 1-136 ^{1}H NMR (101 MHz, $CDCl_3$)



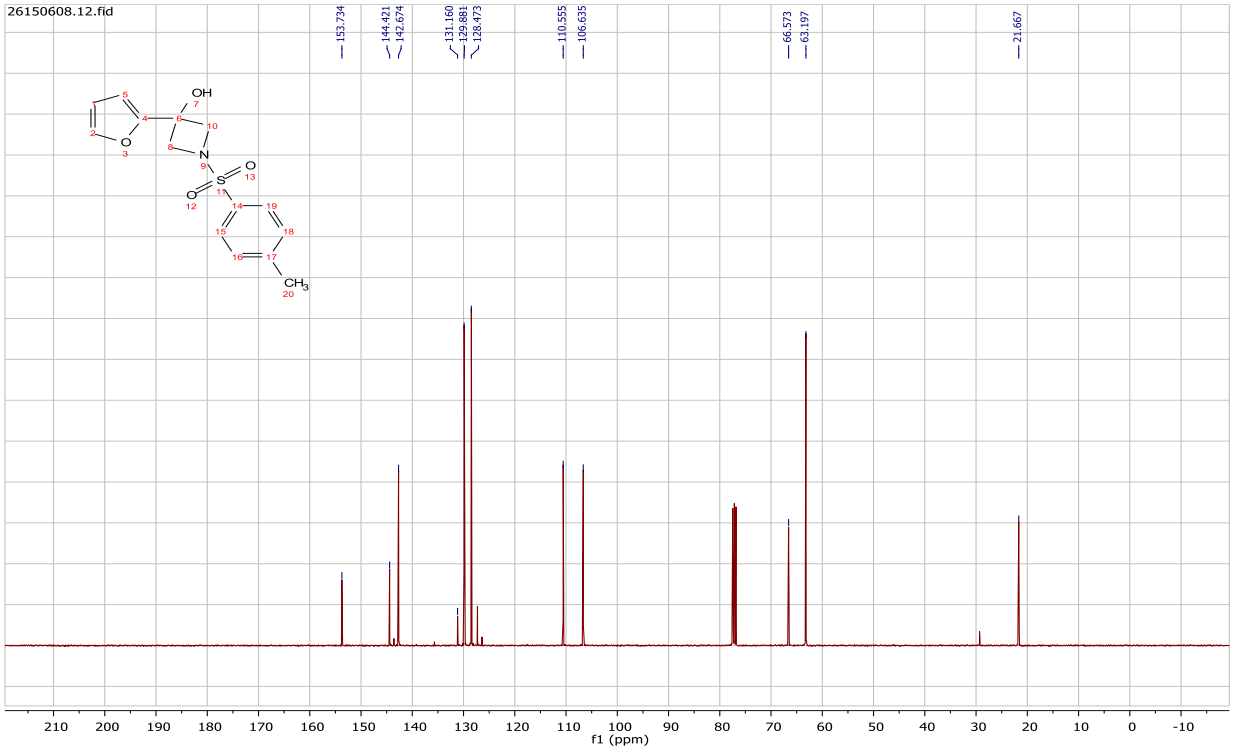
Compound 1-136 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



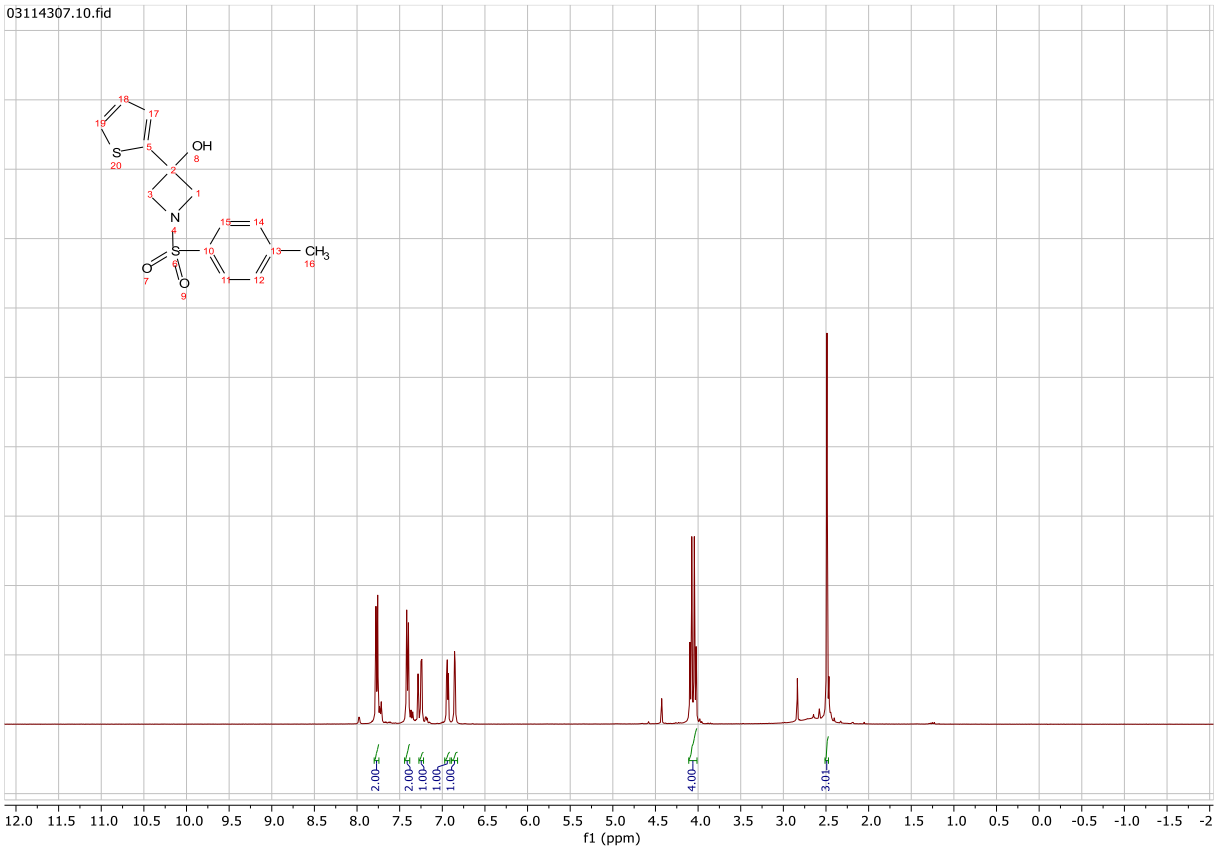
Compound 1-137 ^{1}H NMR (101 MHz, $CDCl_3$)



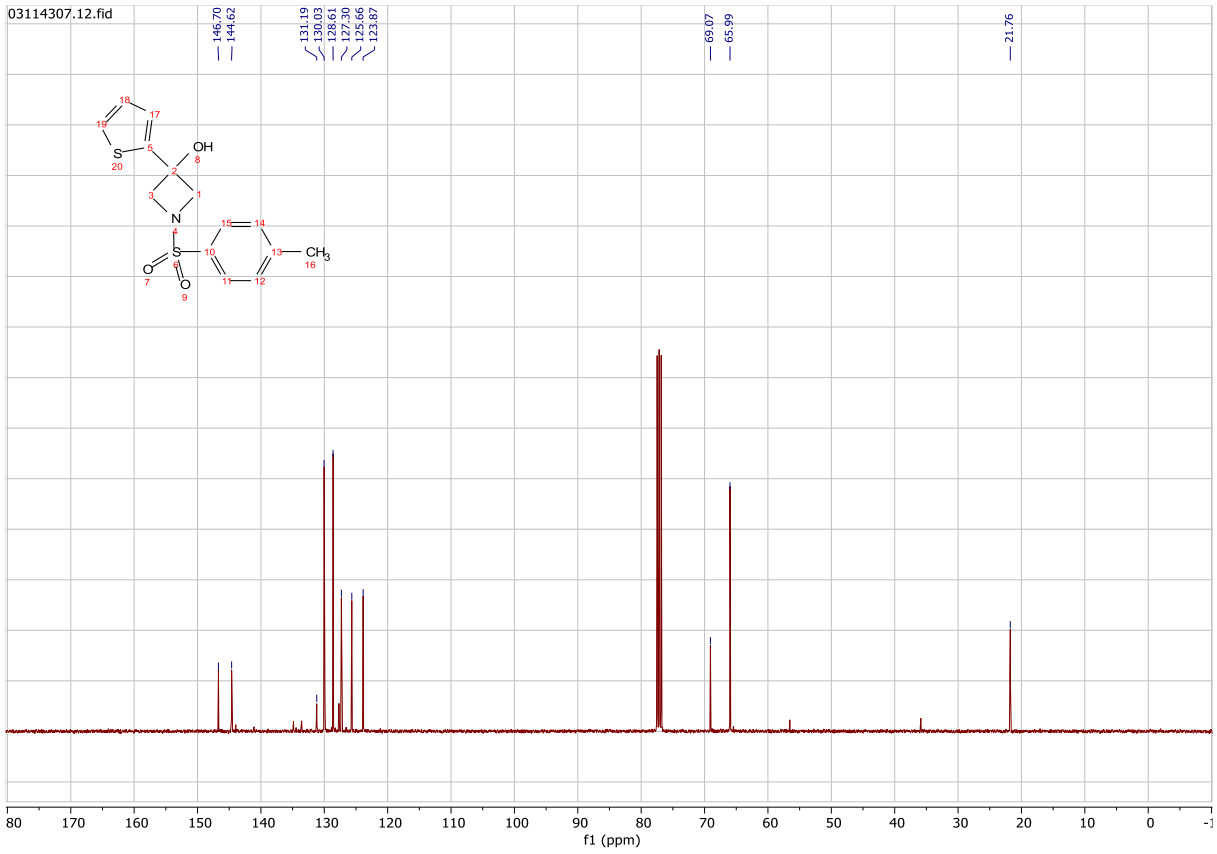
Compound 1-137 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



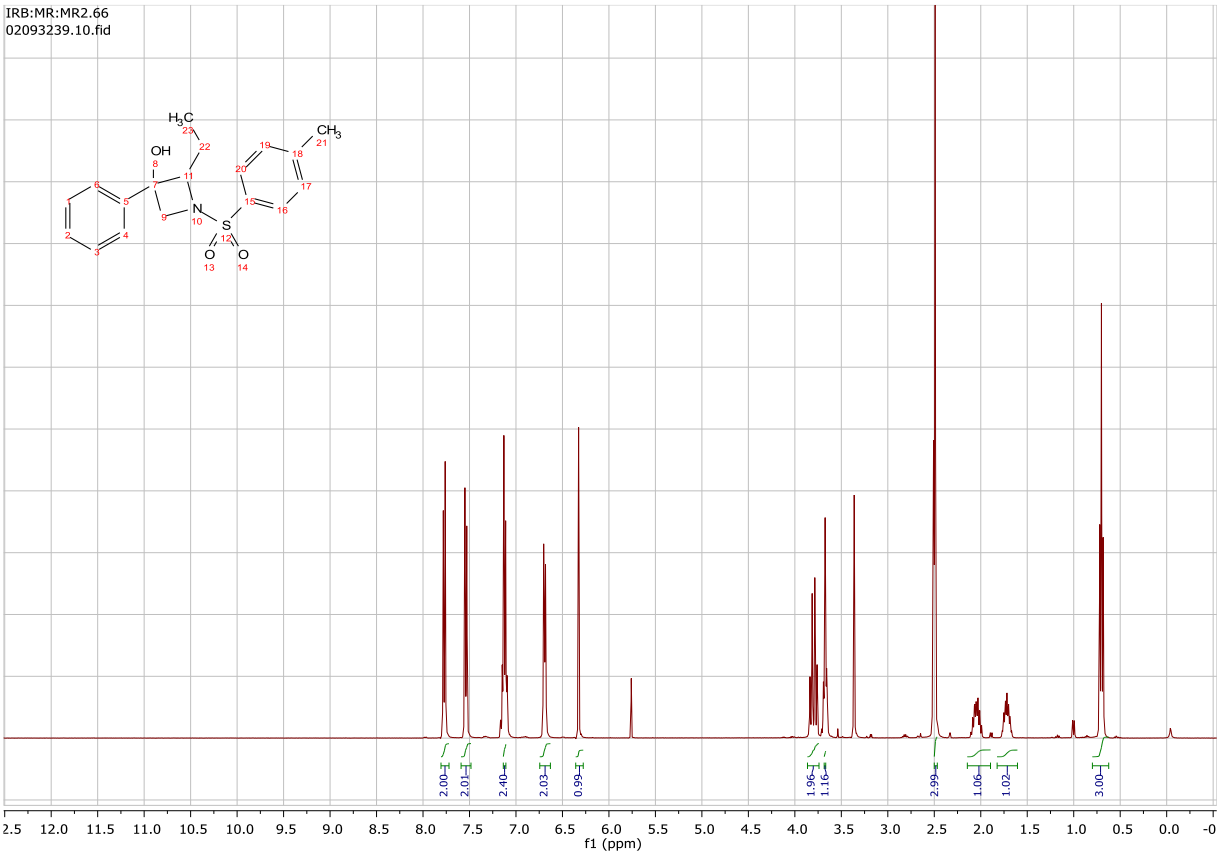
Compound 1-138 ^{1}H NMR (101 MHz, $CDCl_3$)



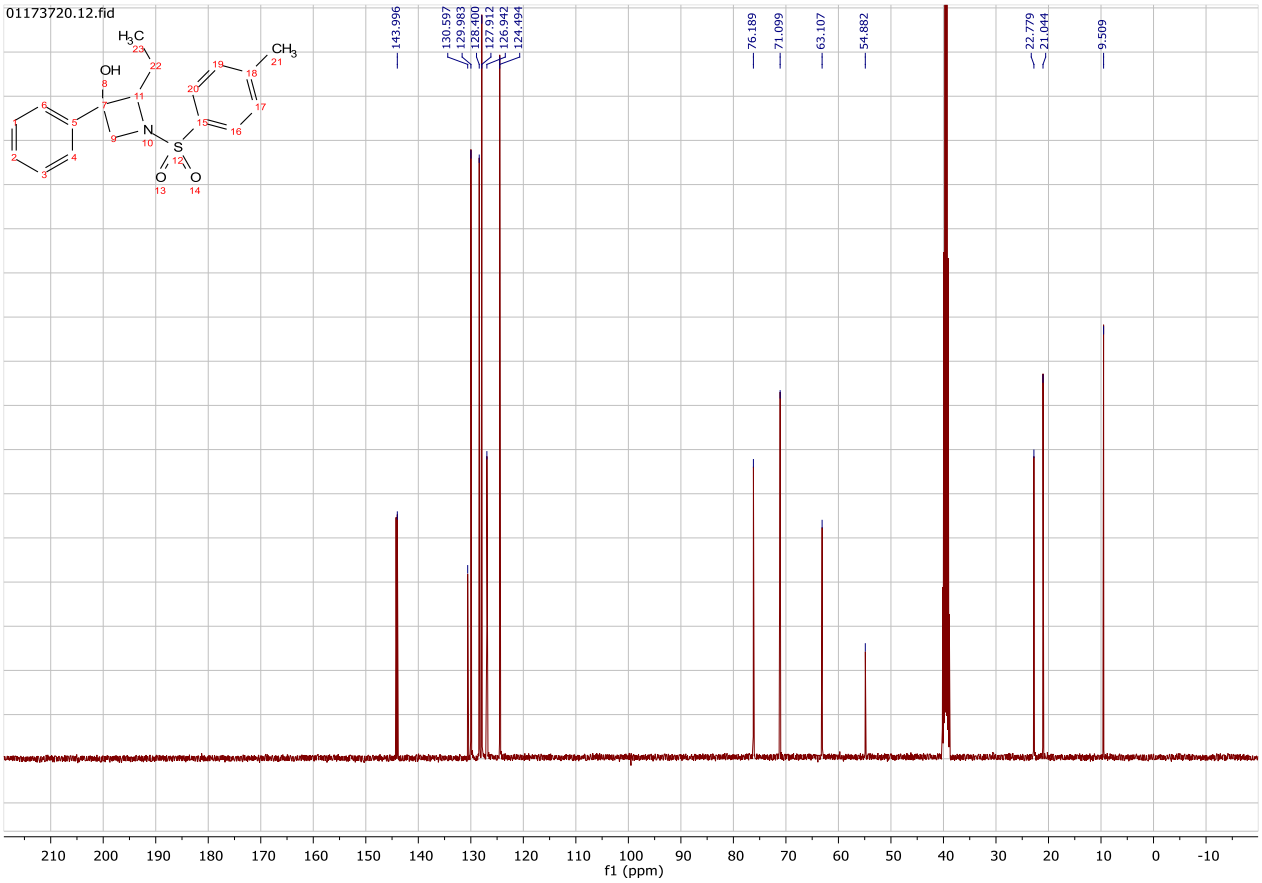
Compound 1-138 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



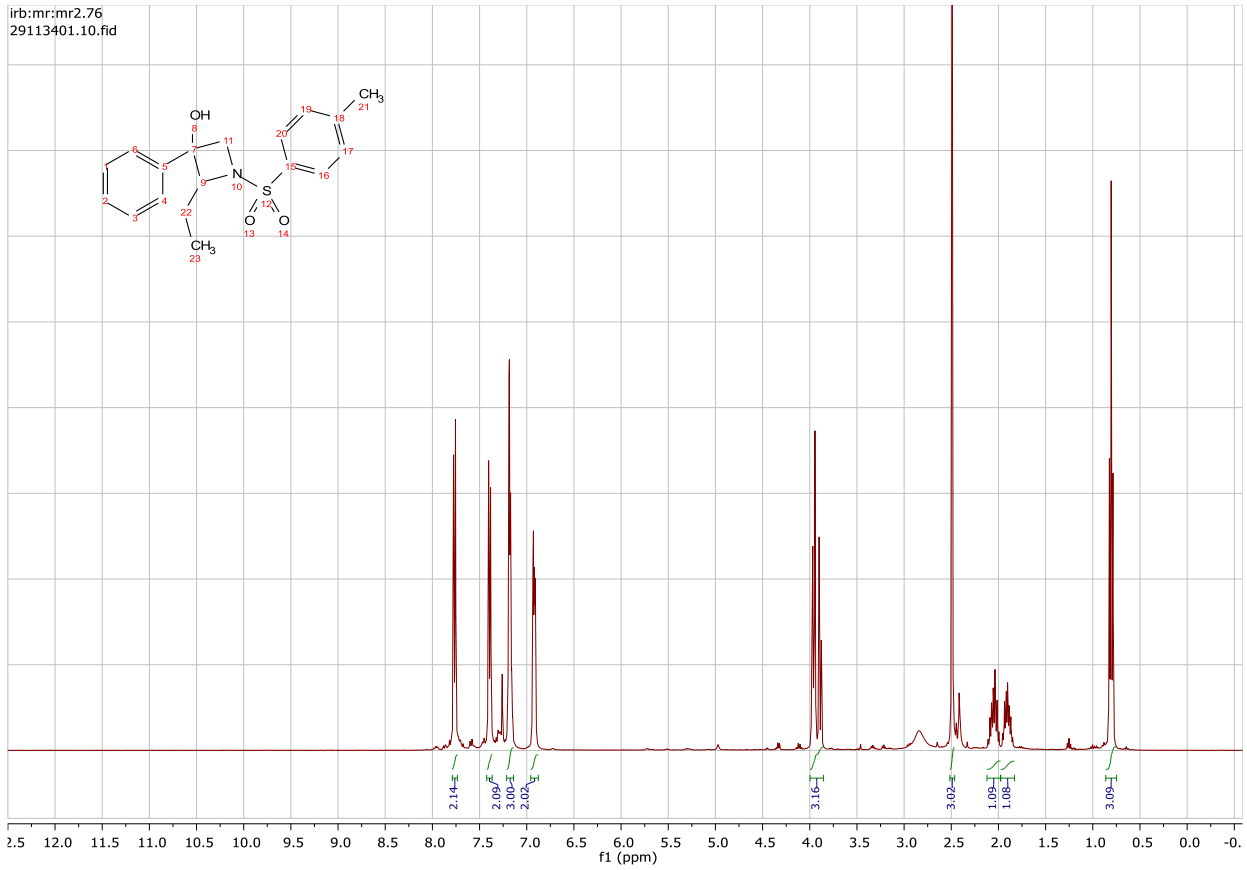
Compound 1-139 ^{1}H NMR (101 MHz, $CDCl_3$)



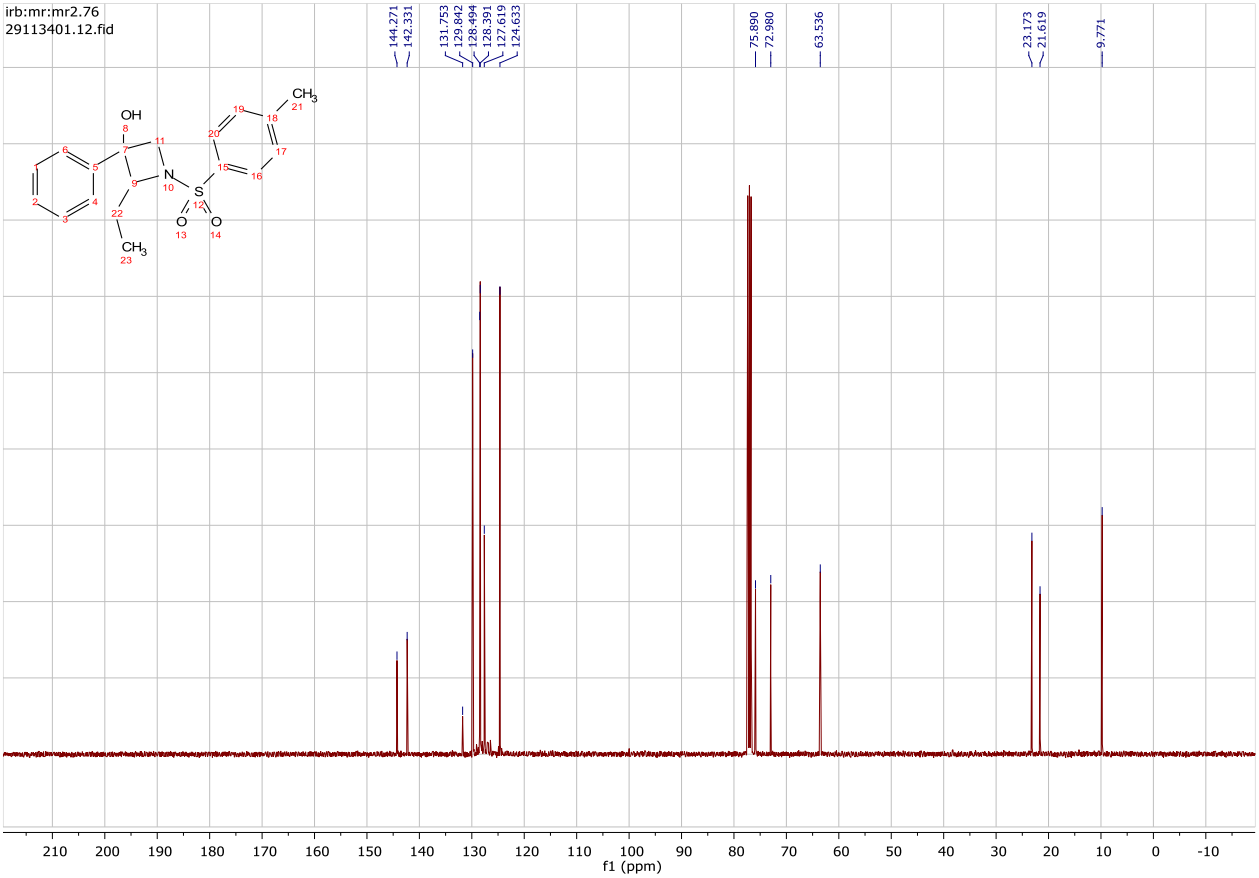
Compound 1-139 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



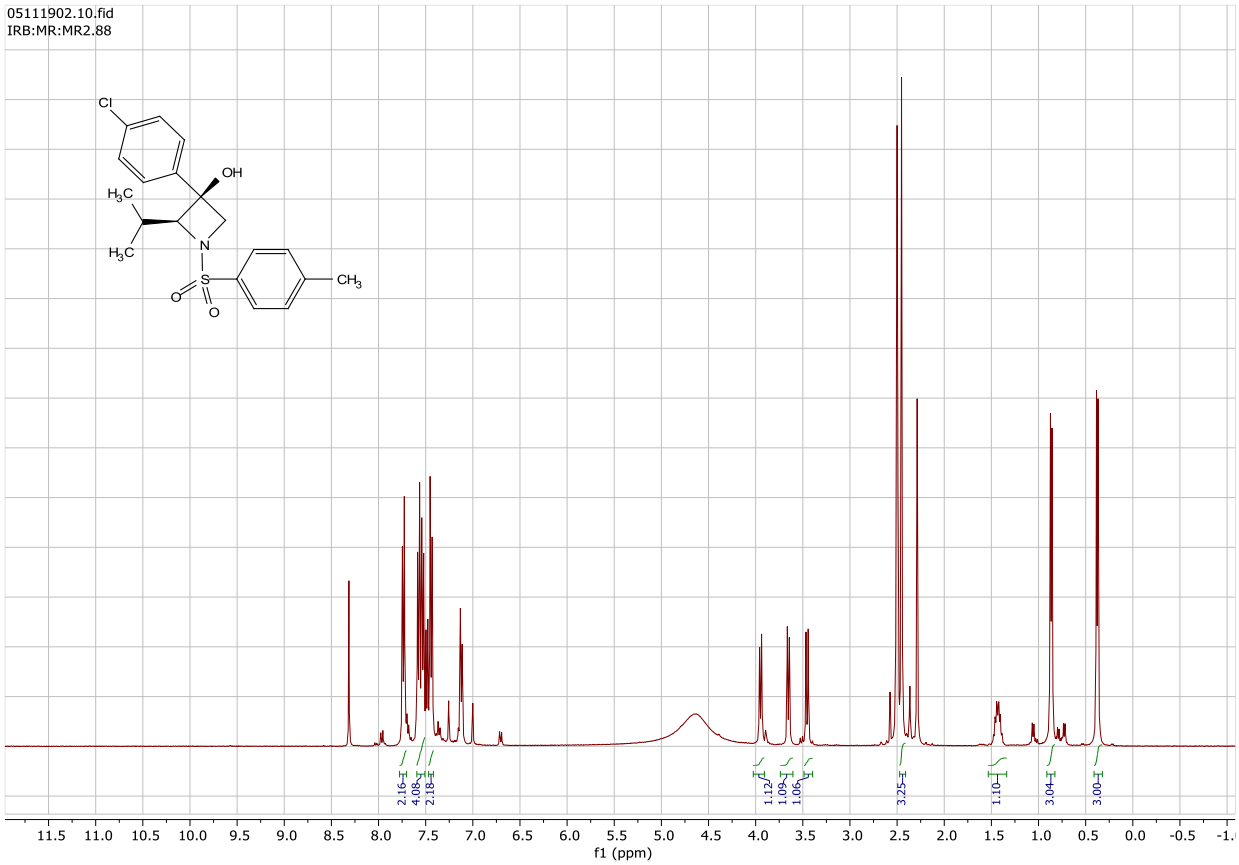
Compound 1-140 ^{1}H NMR (101 MHz, $CDCl_3$)



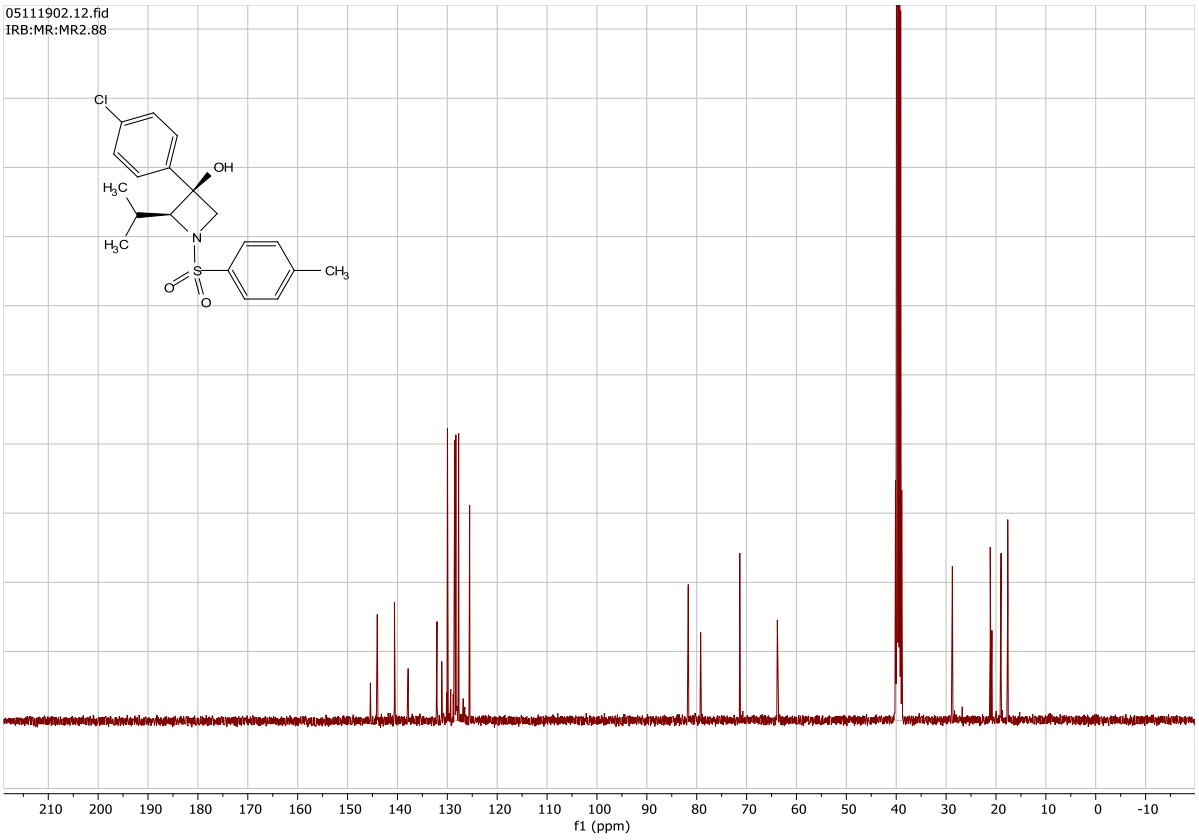
Compound 1-140 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



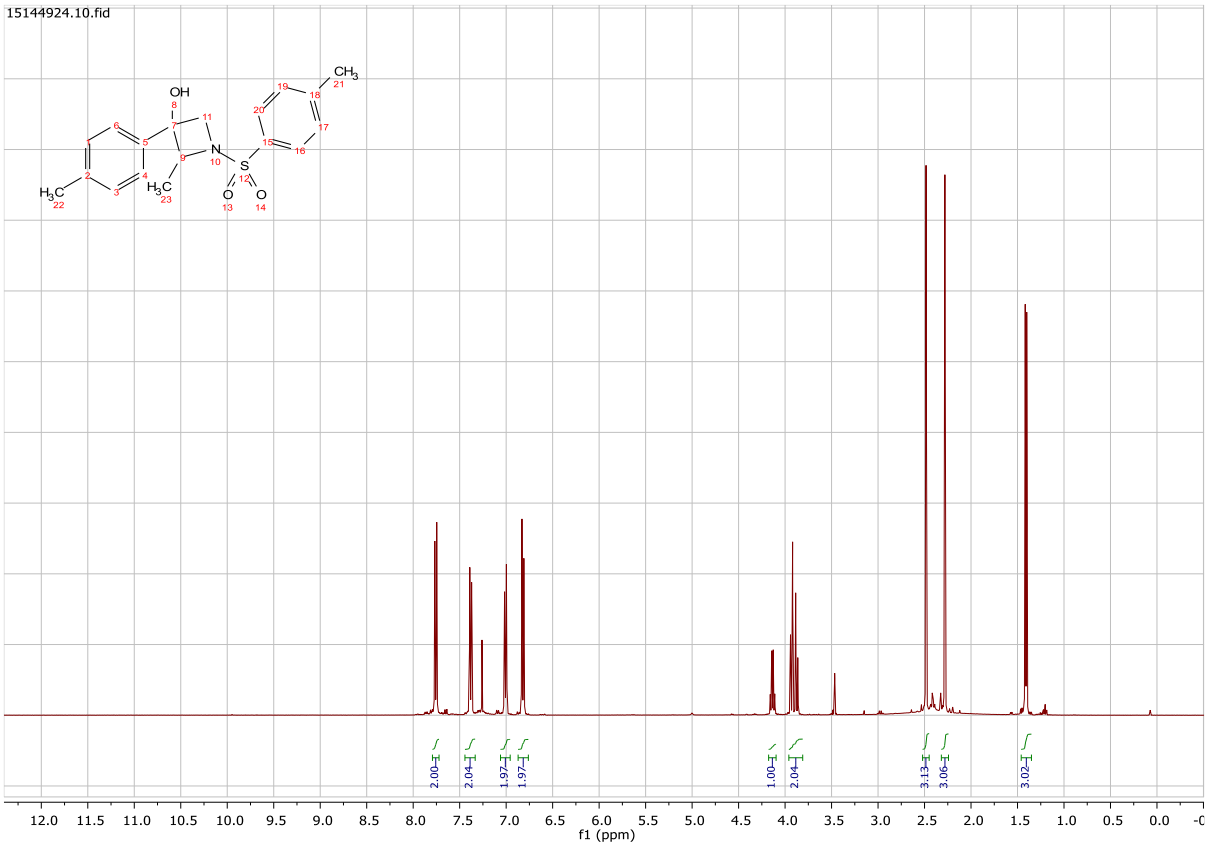
Compound 1-141 ^{1}H NMR (101 MHz, $CDCl_3$)



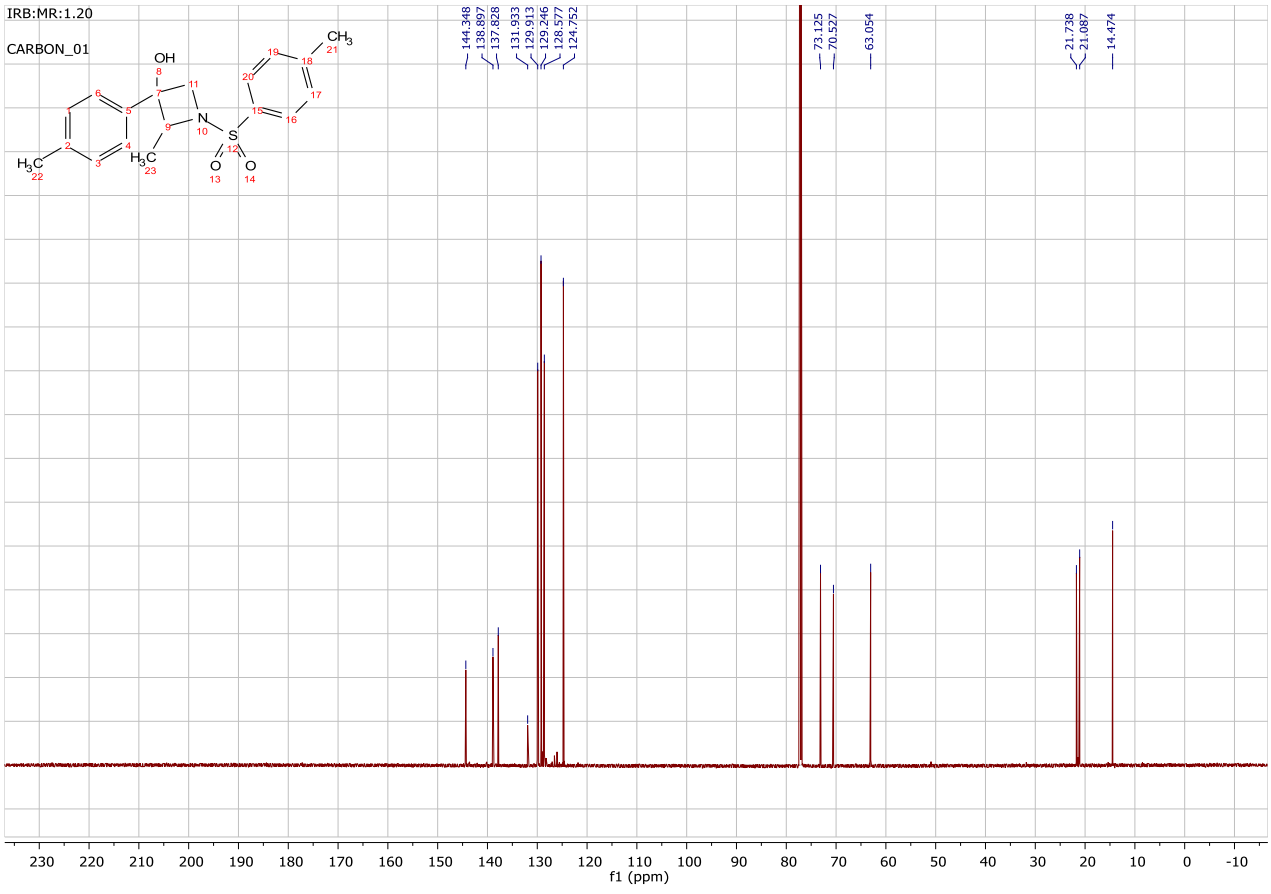
Compound 1-141 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



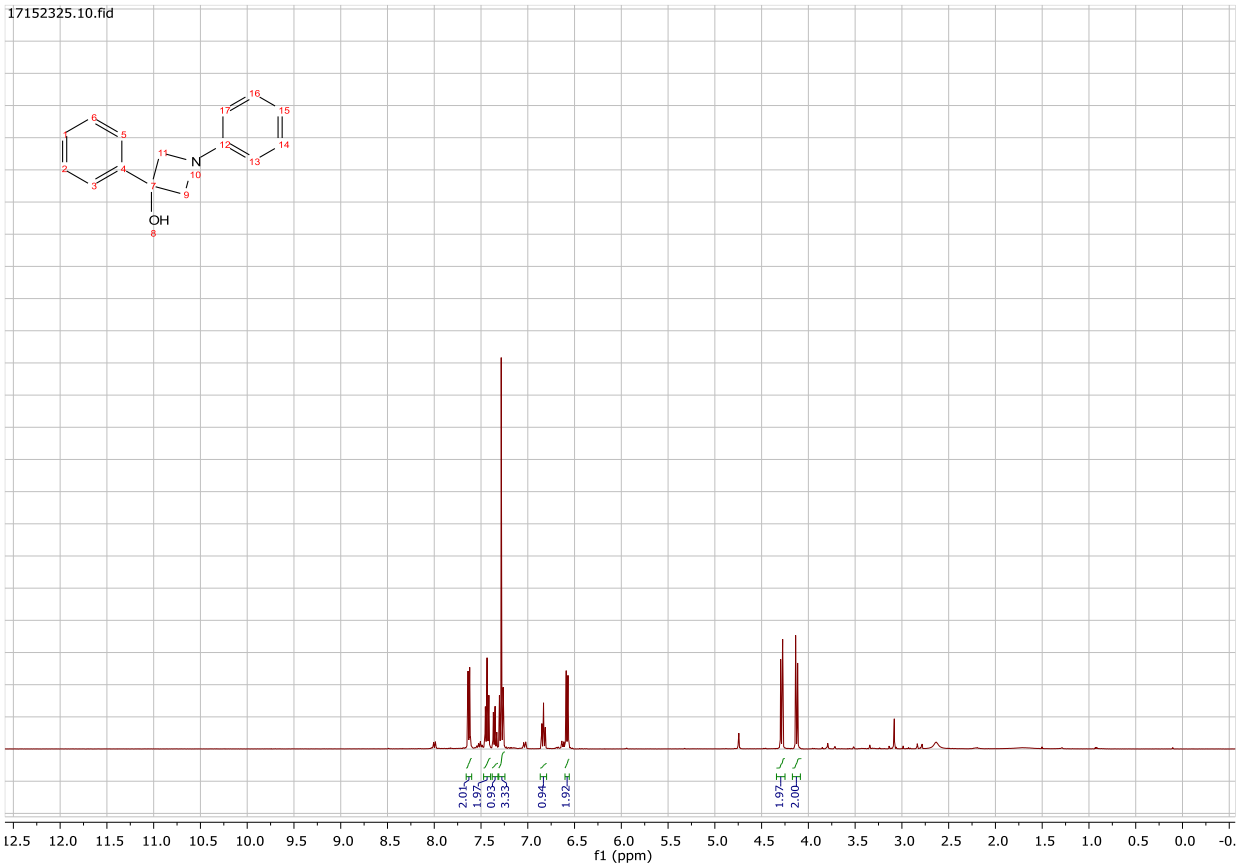
Compound 1-142 ^{1}H NMR (101 MHz, $CDCl_3$)



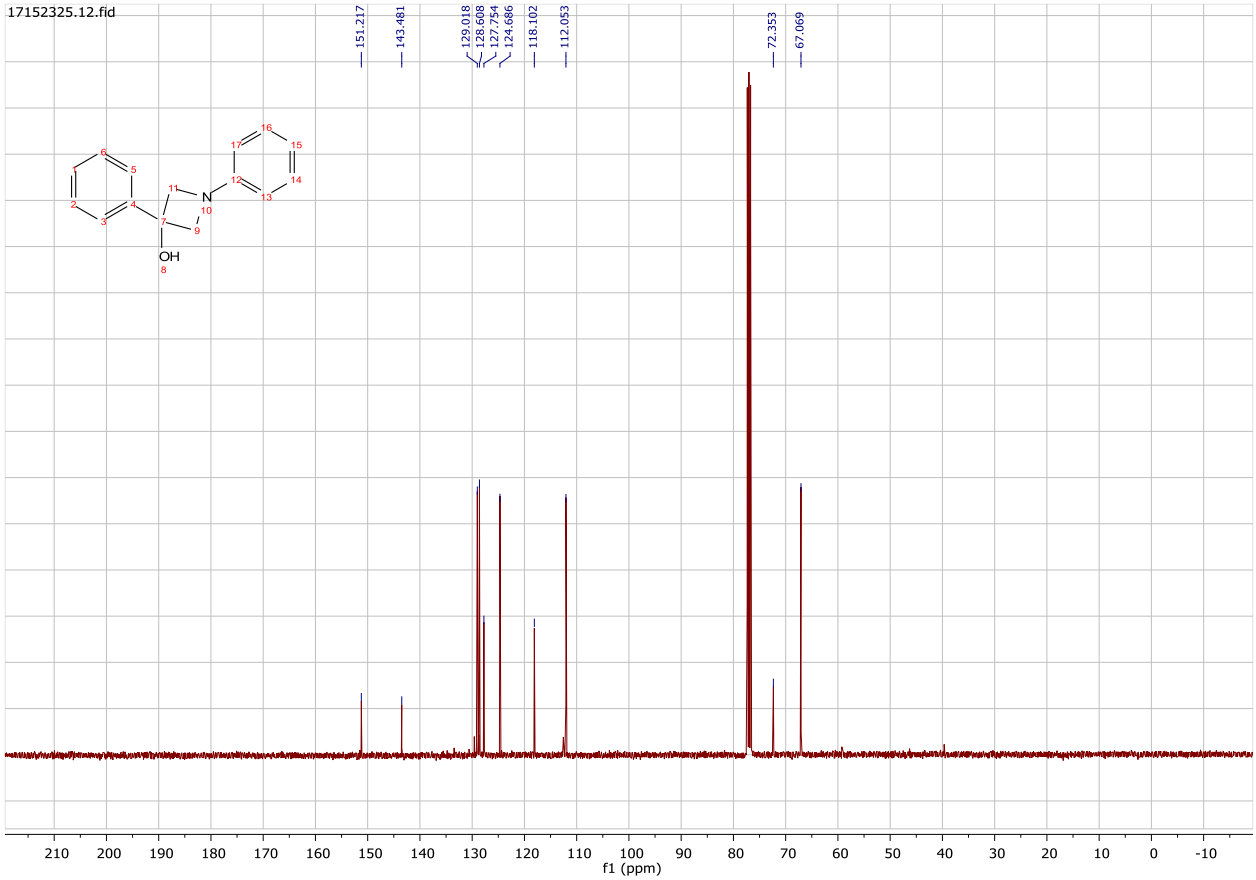
Compound 1-142 $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



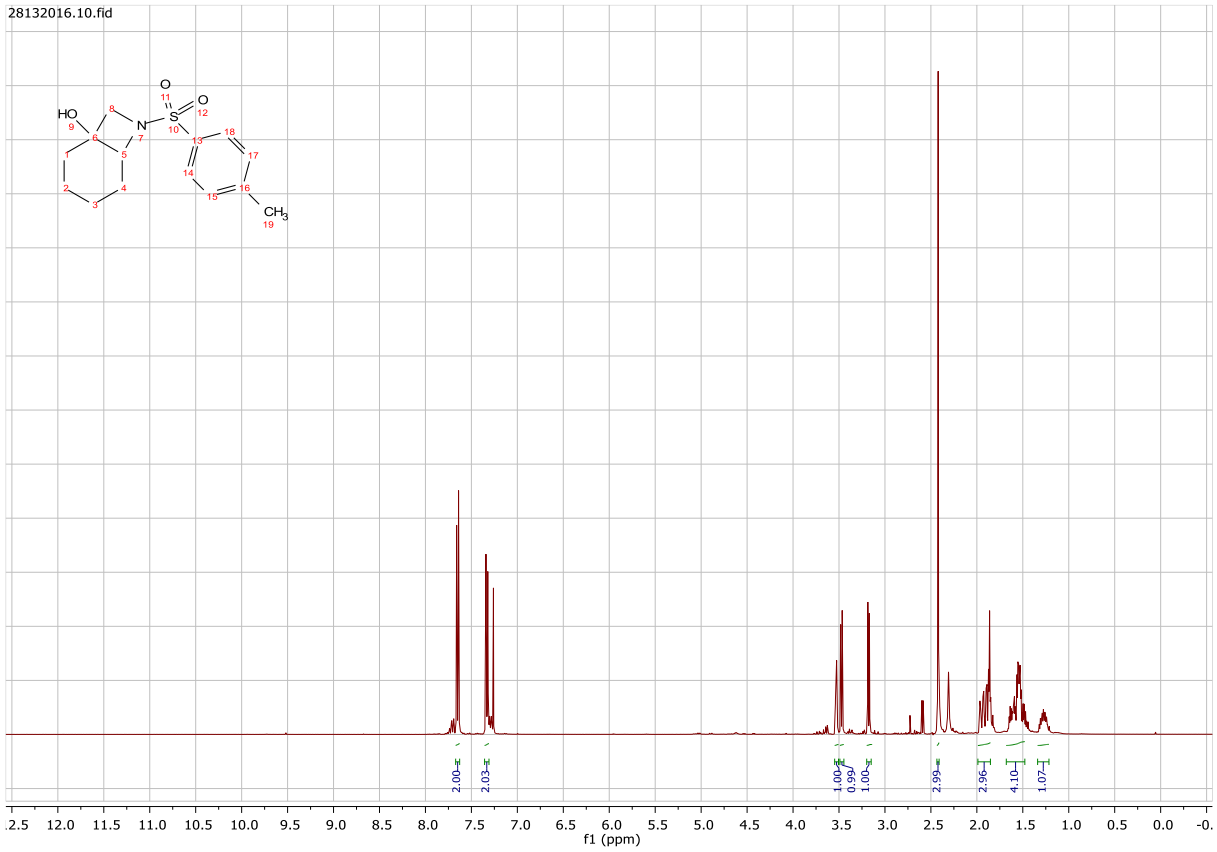
Compound 1-146 ^{1}H NMR (101 MHz, $CDCl_3$)



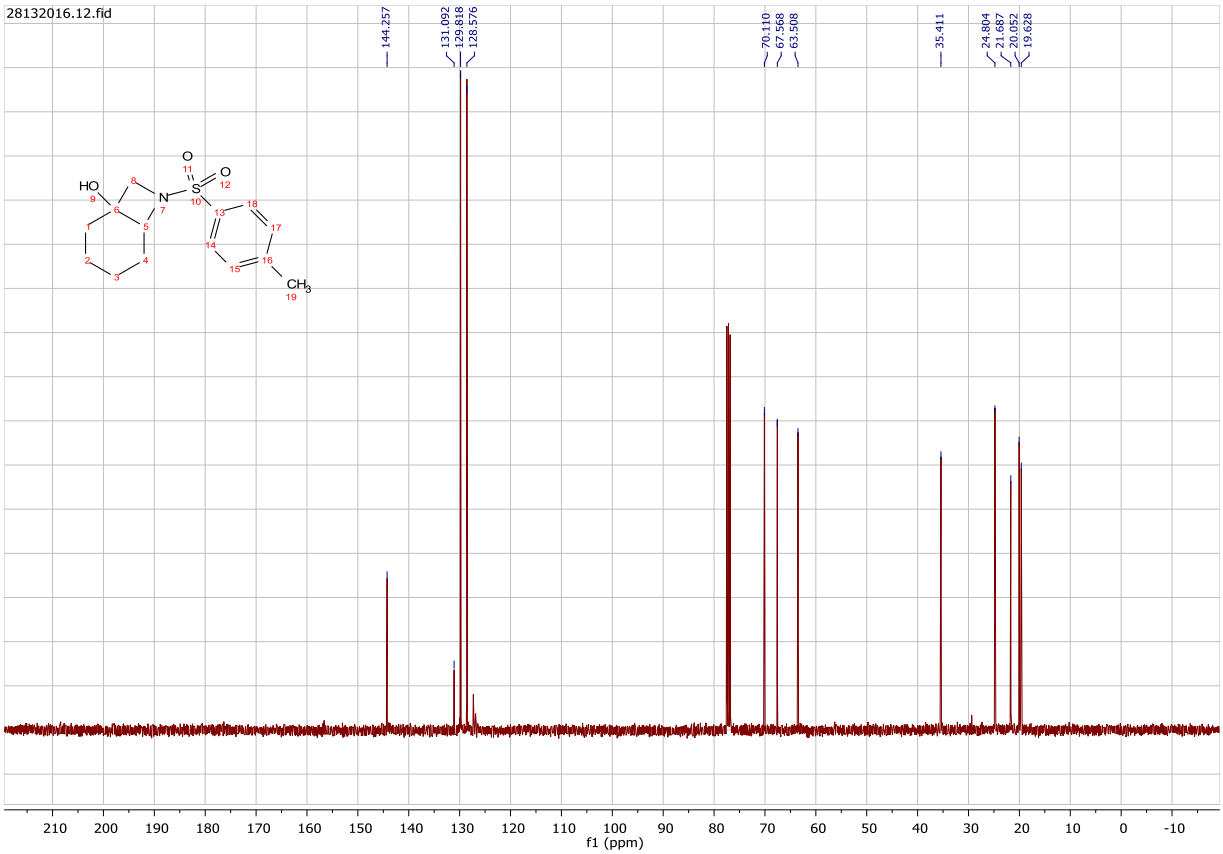
Compound 1-146 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



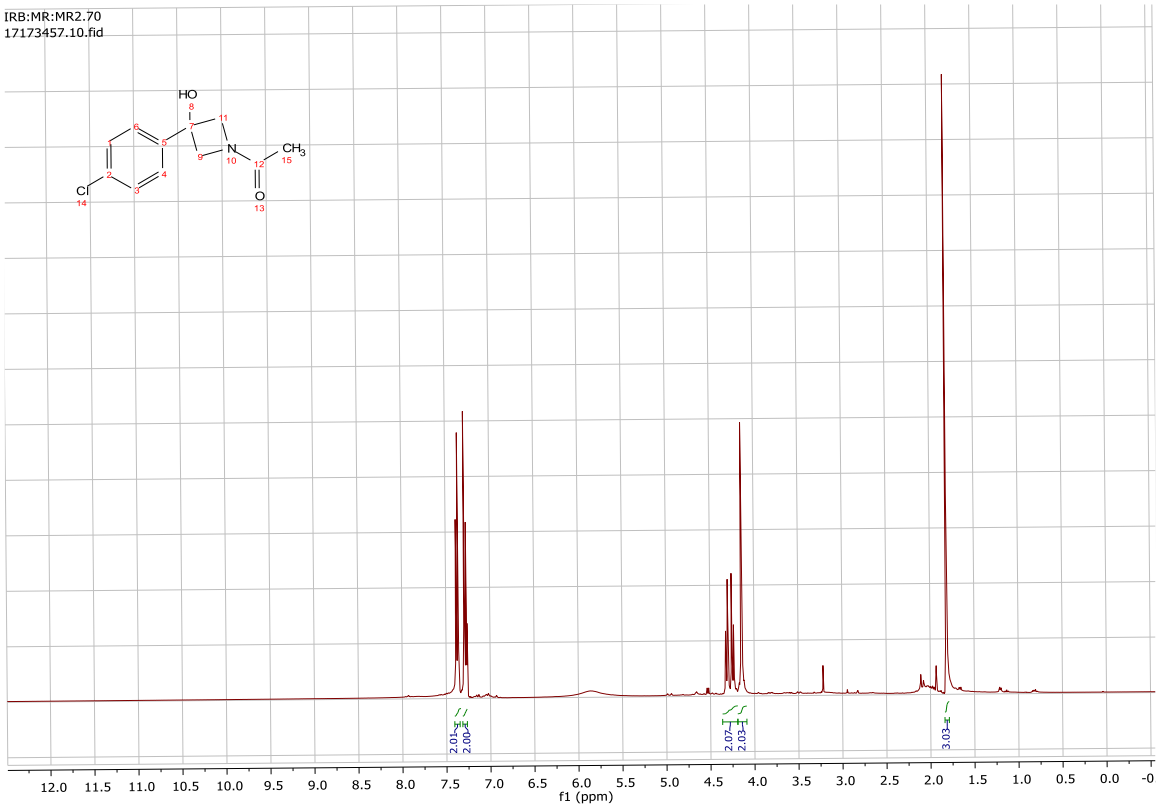
Compound 1-150 ^{1}H NMR (101 MHz, $CDCl_3$)



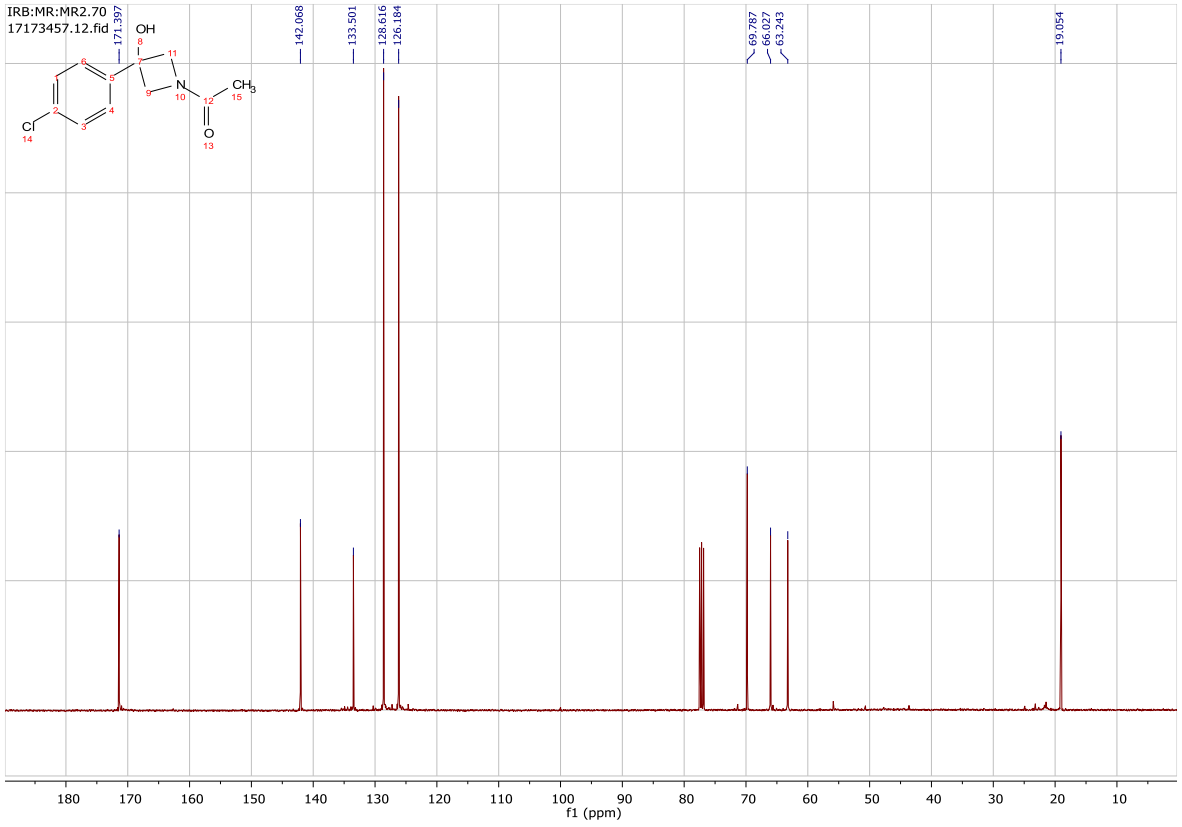
Compound 1-150 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



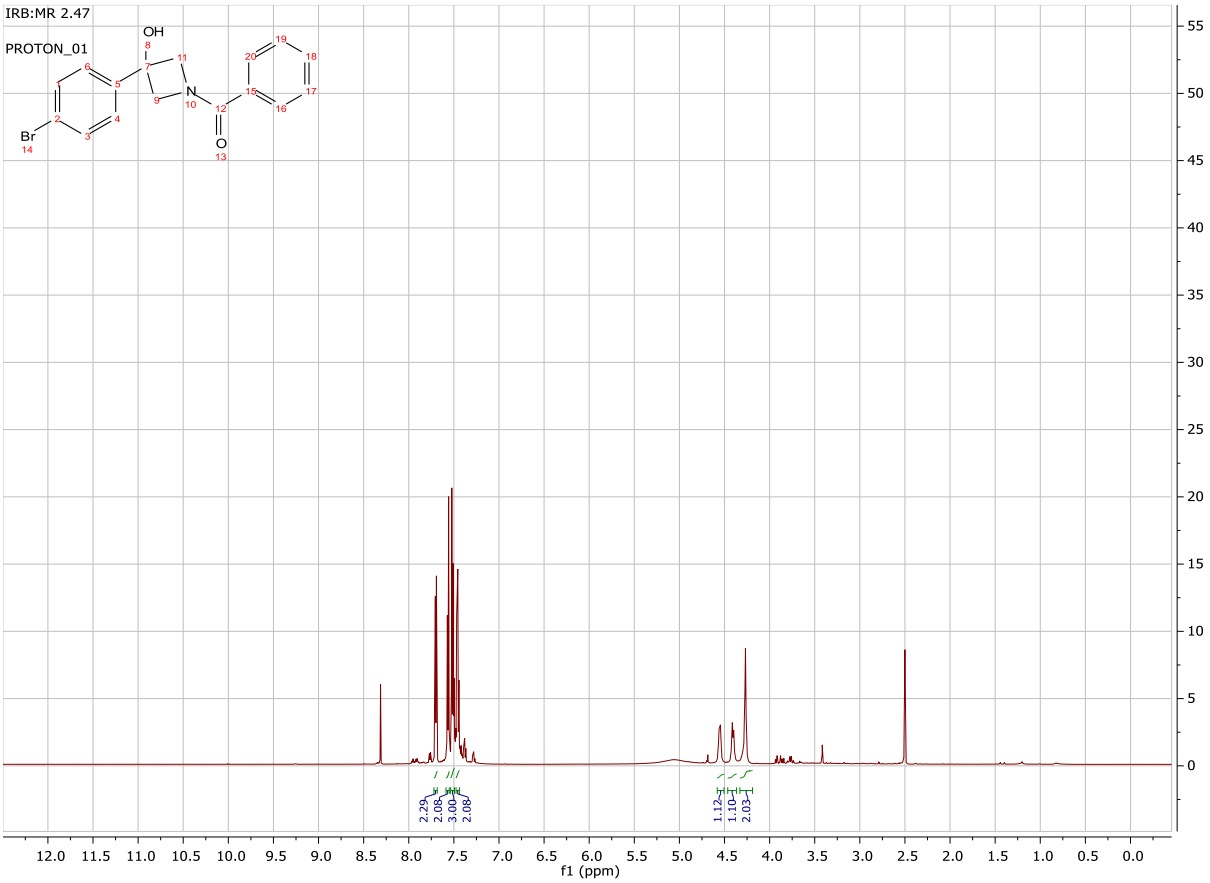
Compound 1-156 ^{1}H NMR (101 MHz, $CDCl_3$)



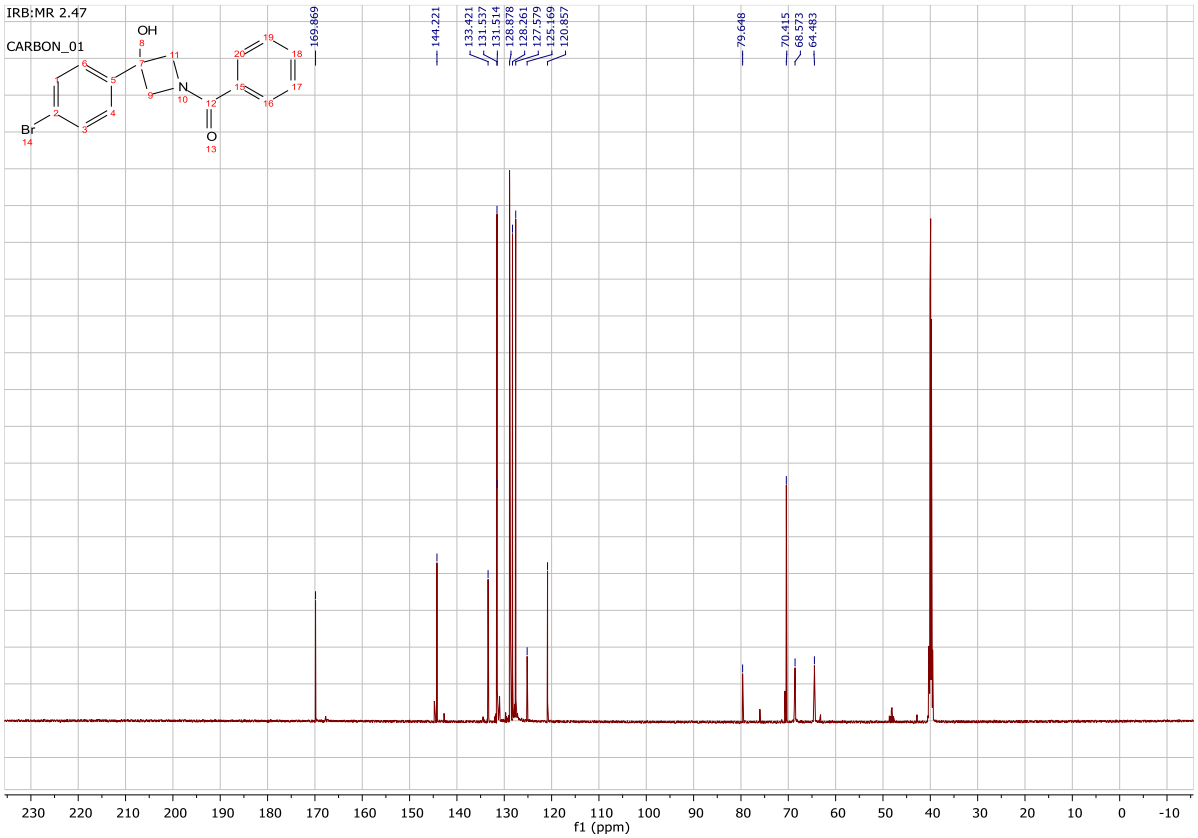
Compound 1-156 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



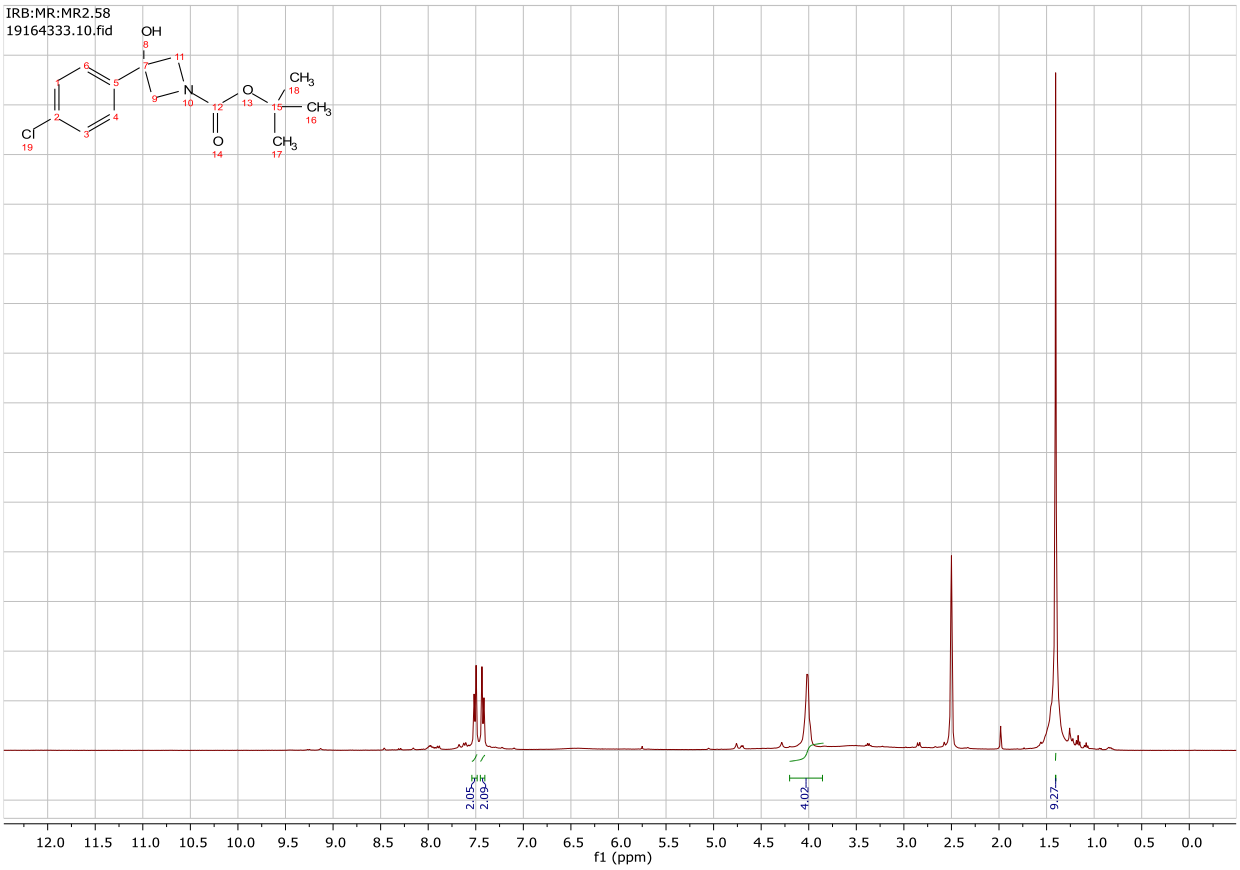
Compound 1-157 ^{1}H NMR (101 MHz, $CDCl_3$)



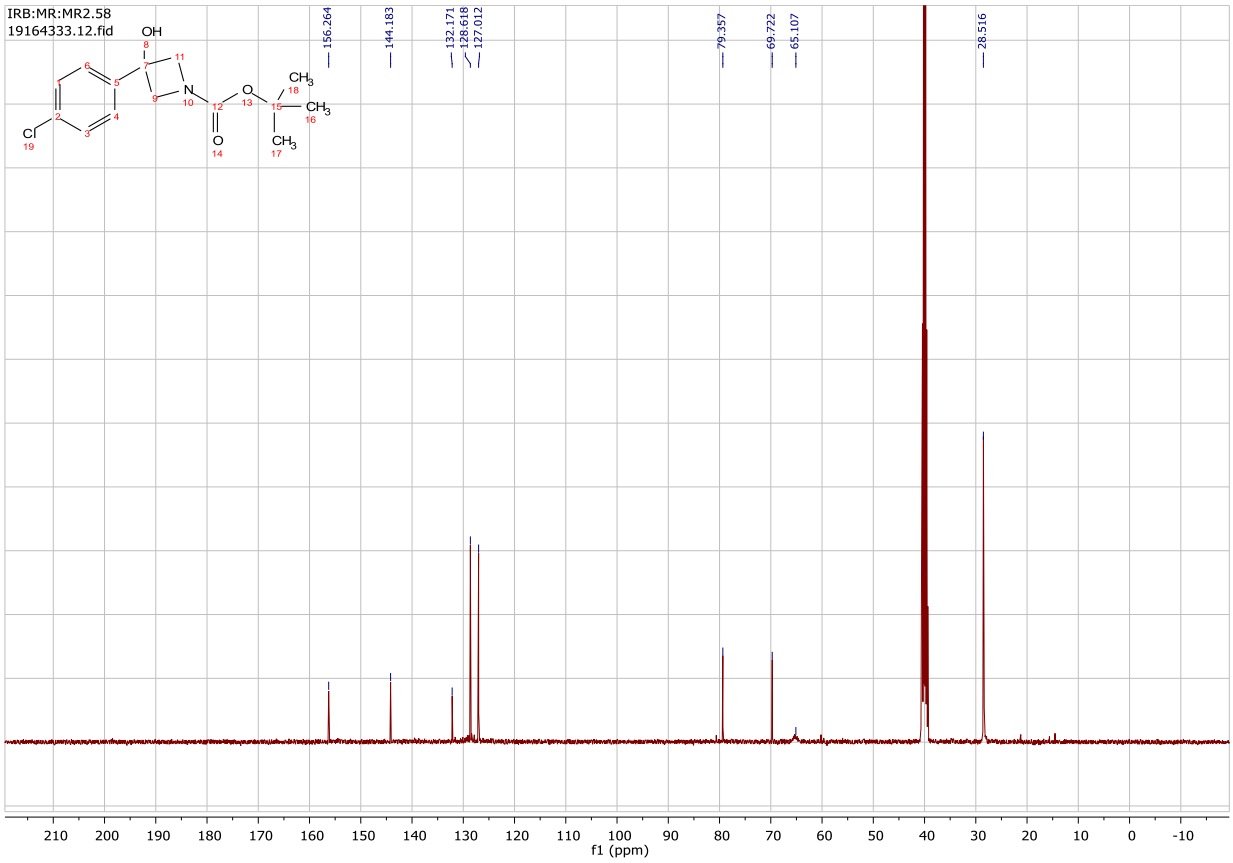
Compound 1-157 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



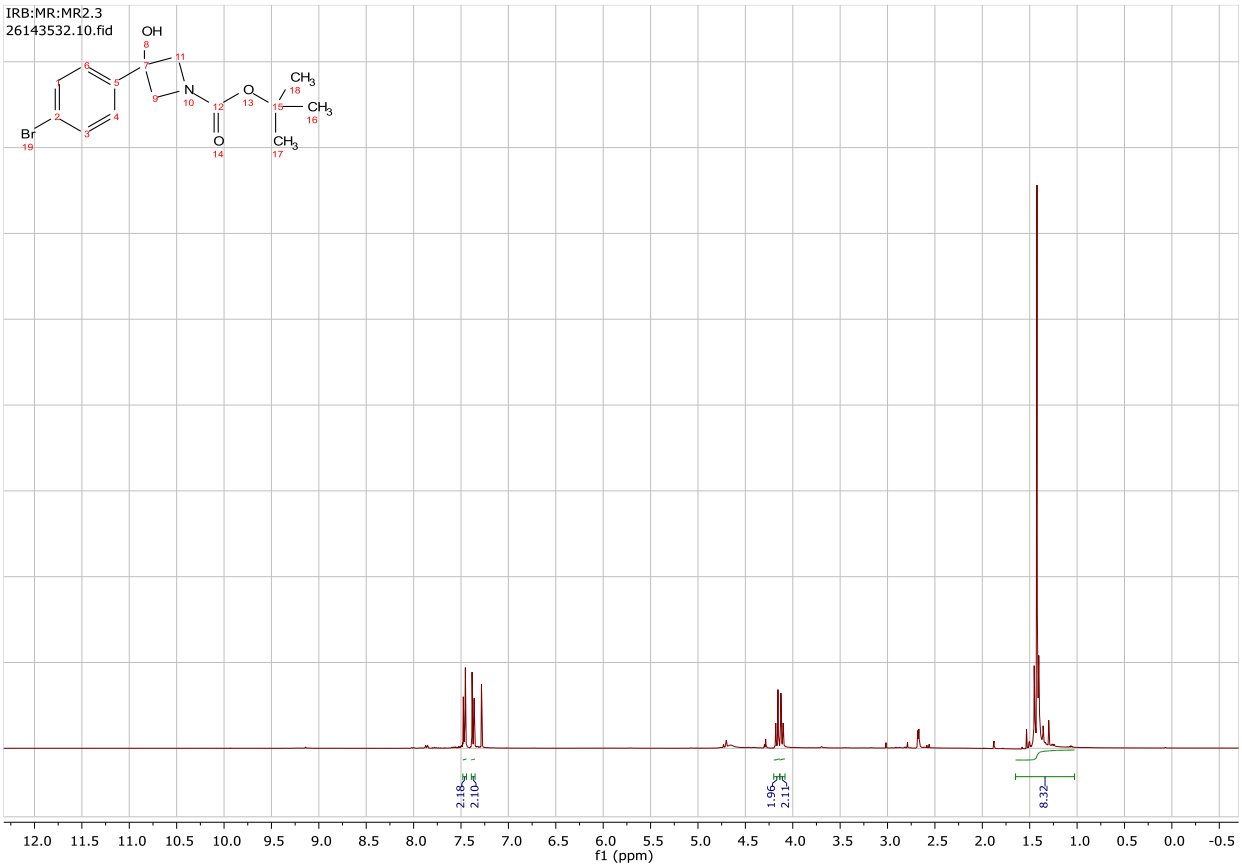
Compound 1-154 ^{1}H NMR (101 MHz, $CDCl_3$)



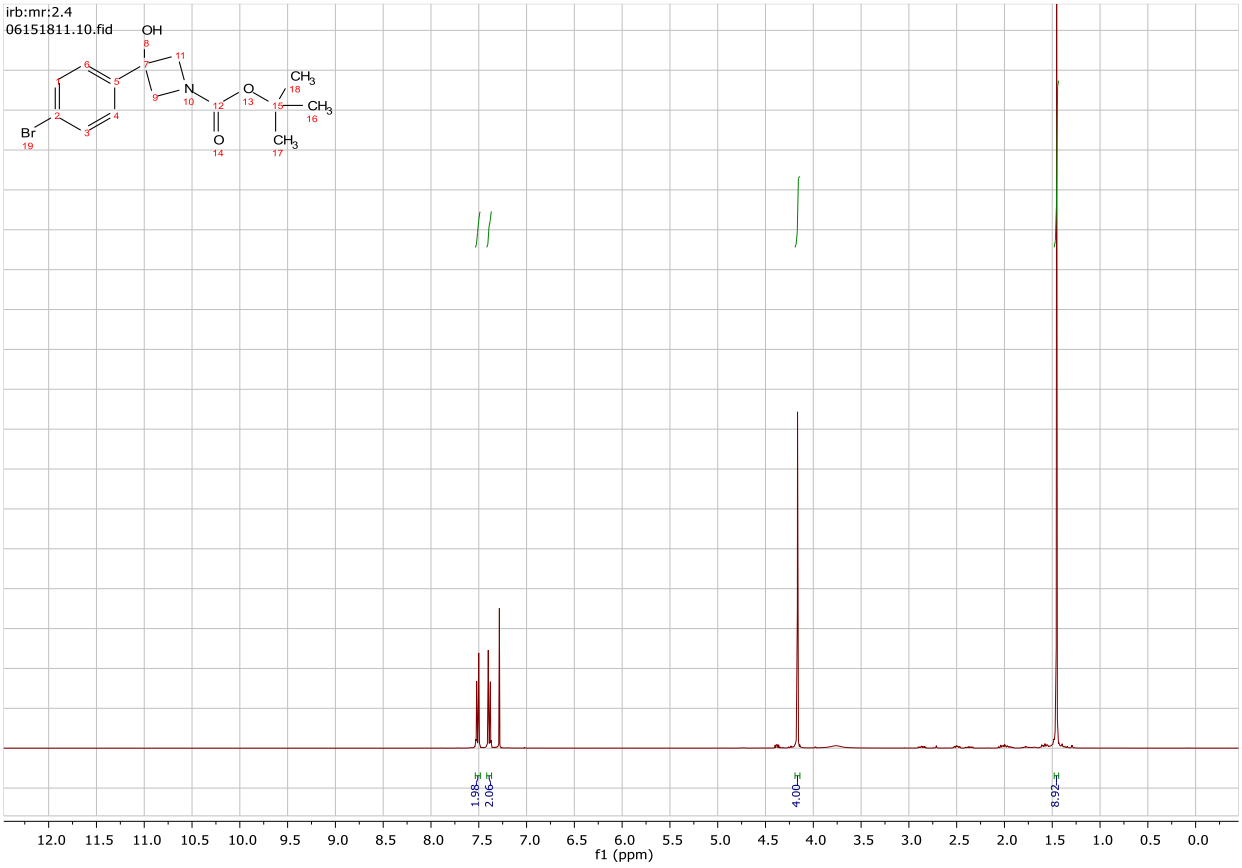
Compound 1-154 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



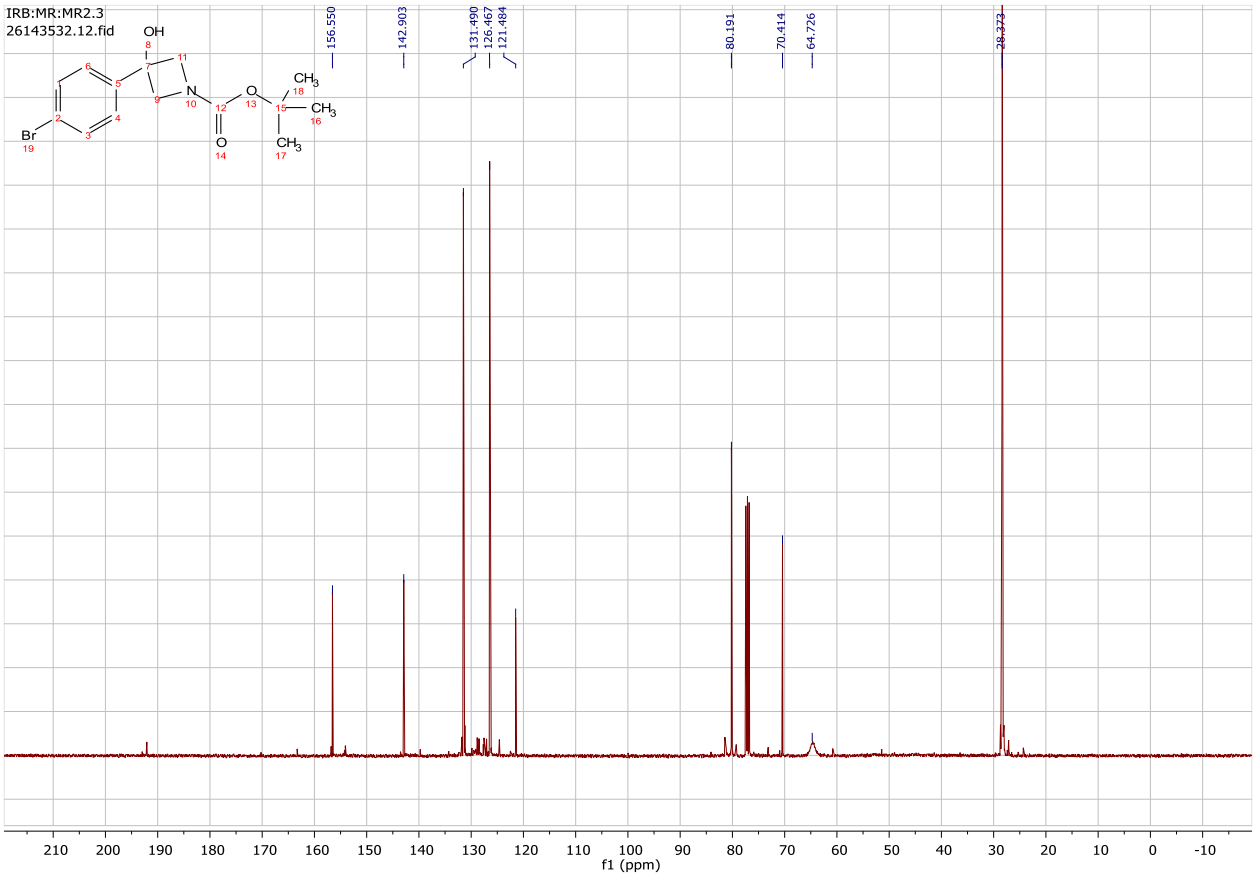
Compound 1-155 ^{1}H NMR (101 MHz, $CDCl_3$)



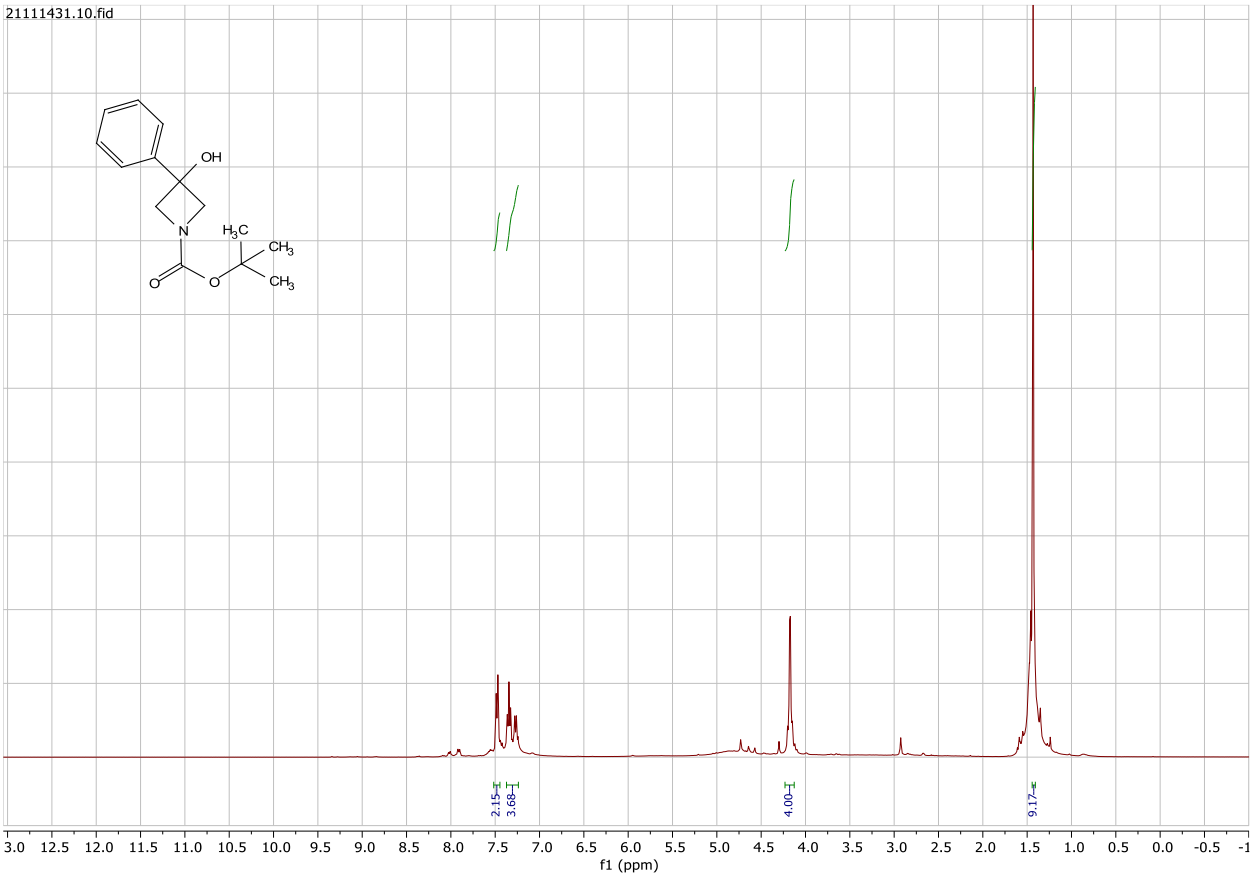
Compound 1-155 ^{1}H NMR (101 MHz, $CDCl_3$)



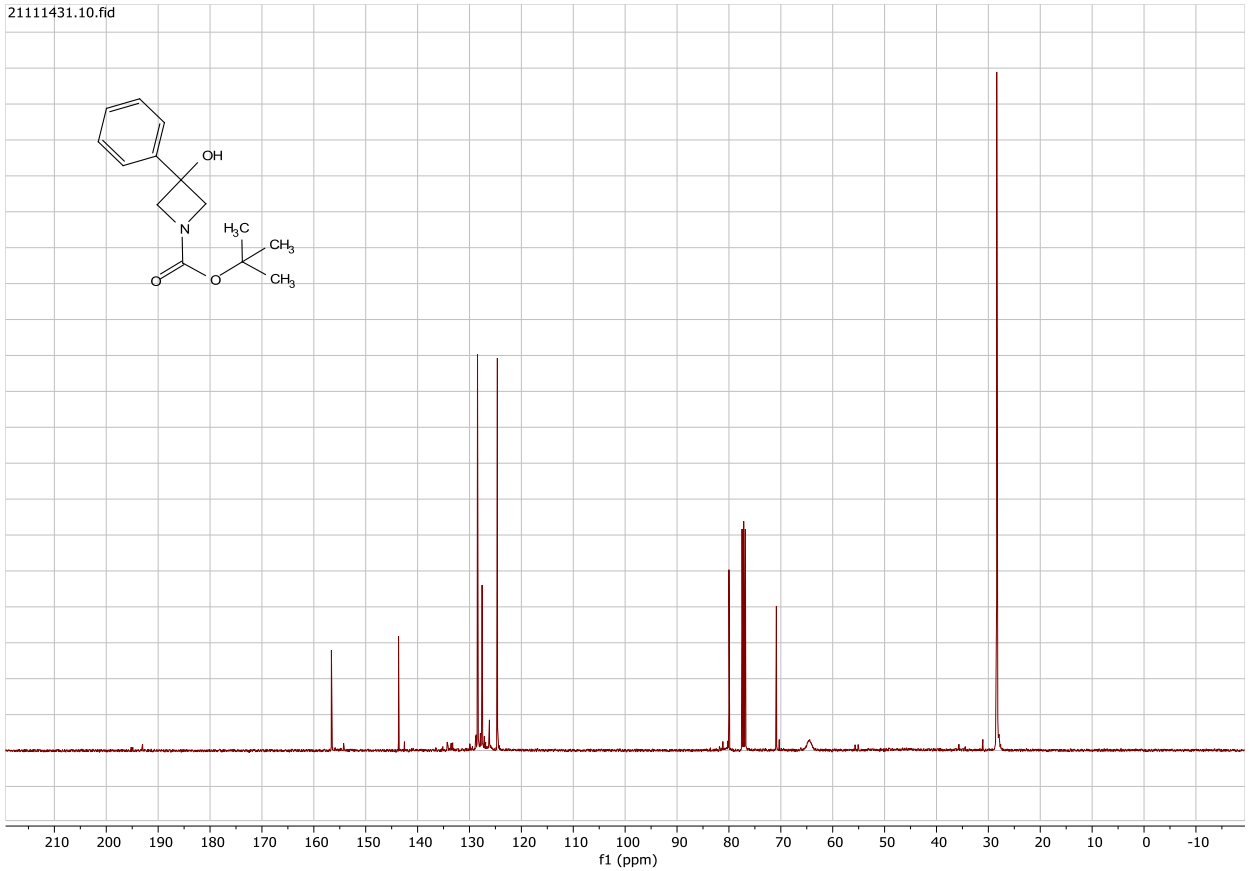
Compound 1-155 $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



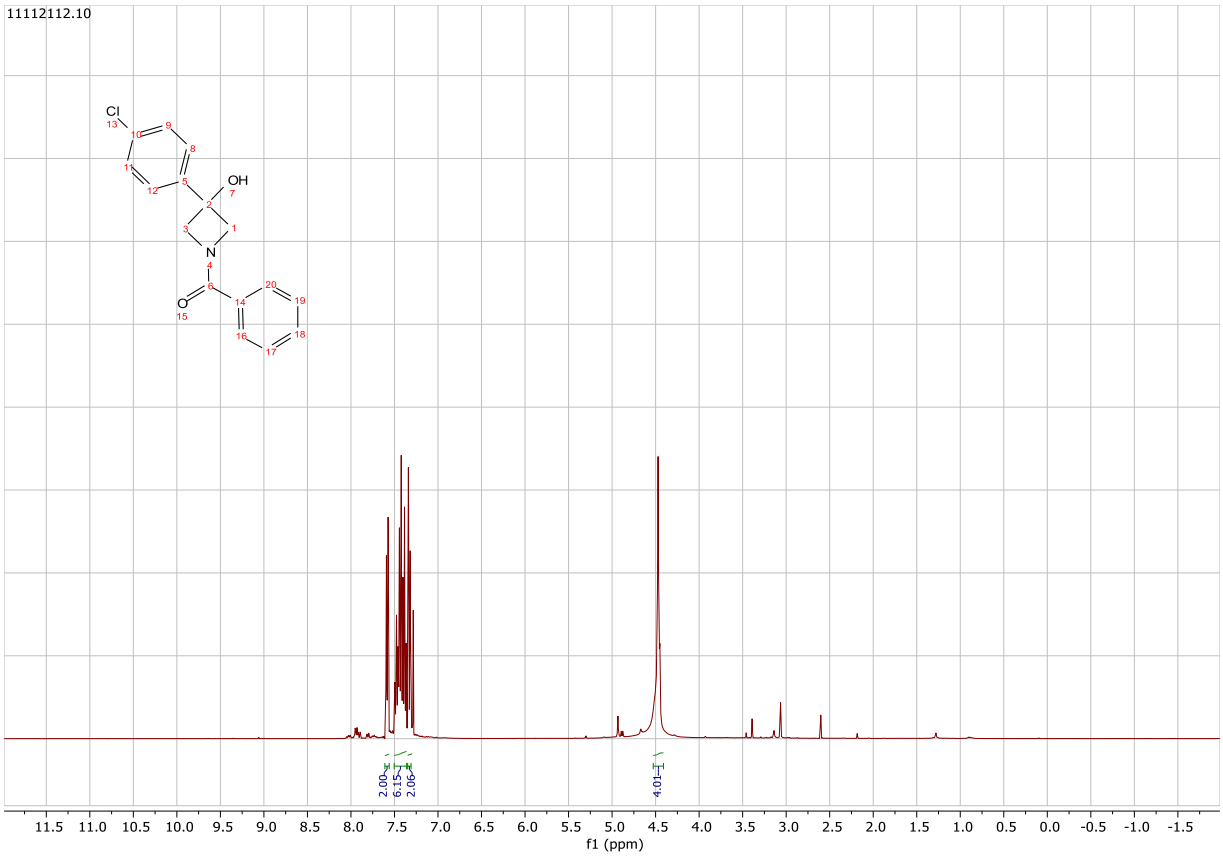
Compound 1-153 ^{1}H NMR (101 MHz, $CDCl_3$)



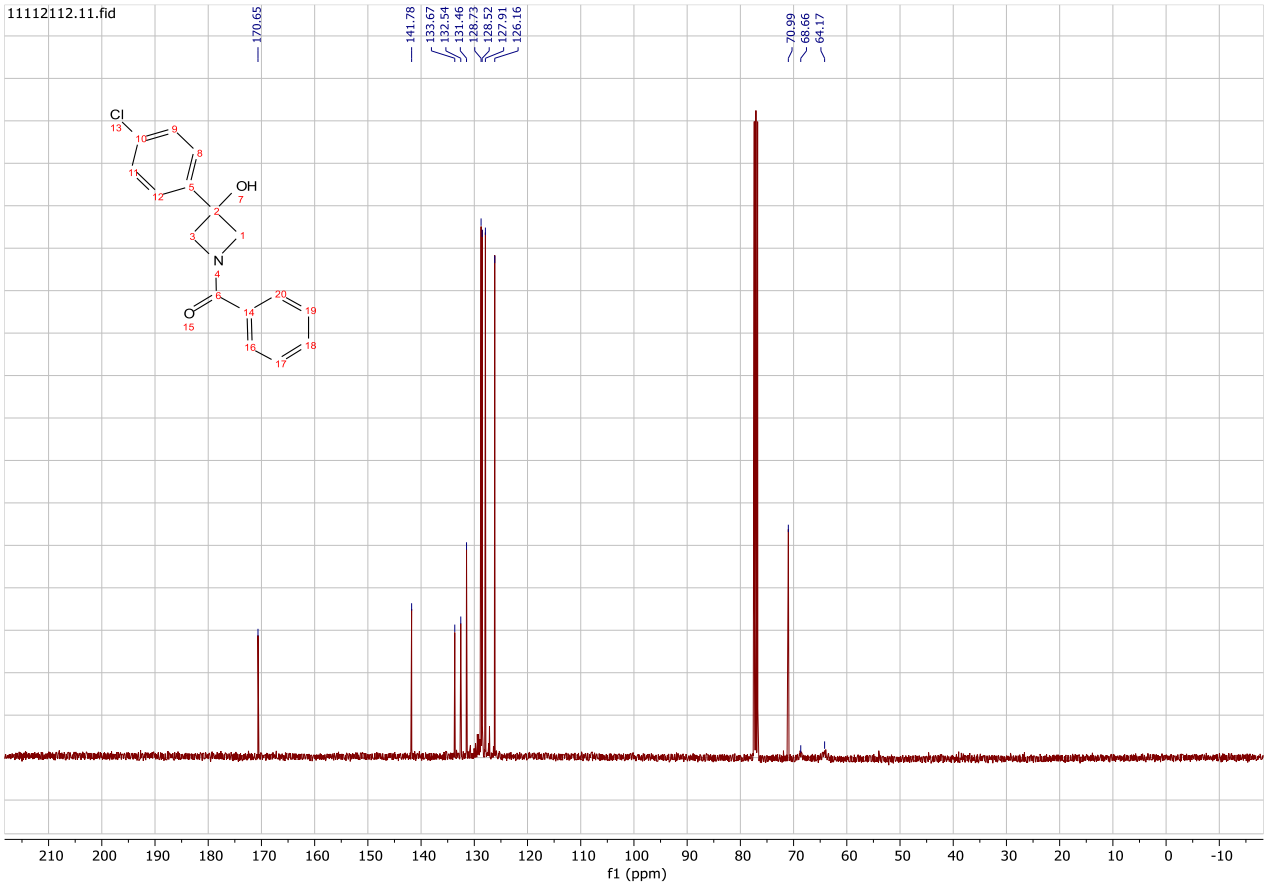
Compound 1-153 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



Compound 1-158 ^{1}H NMR (101 MHz, $CDCl_3$)



Compound 1-158 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



9. References

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[2] R. W. Adams, C. M. Holroyd, J. A. Aguilar, M. Nilsson, G. A. Morris, *Chem. Commun.* ***2013****, 49*, 358–360.

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[4] N. Ishida, Y. Shimamoto, M. Murakami, *Angew. Chem.* **2012**, *51*, 11750−1175.

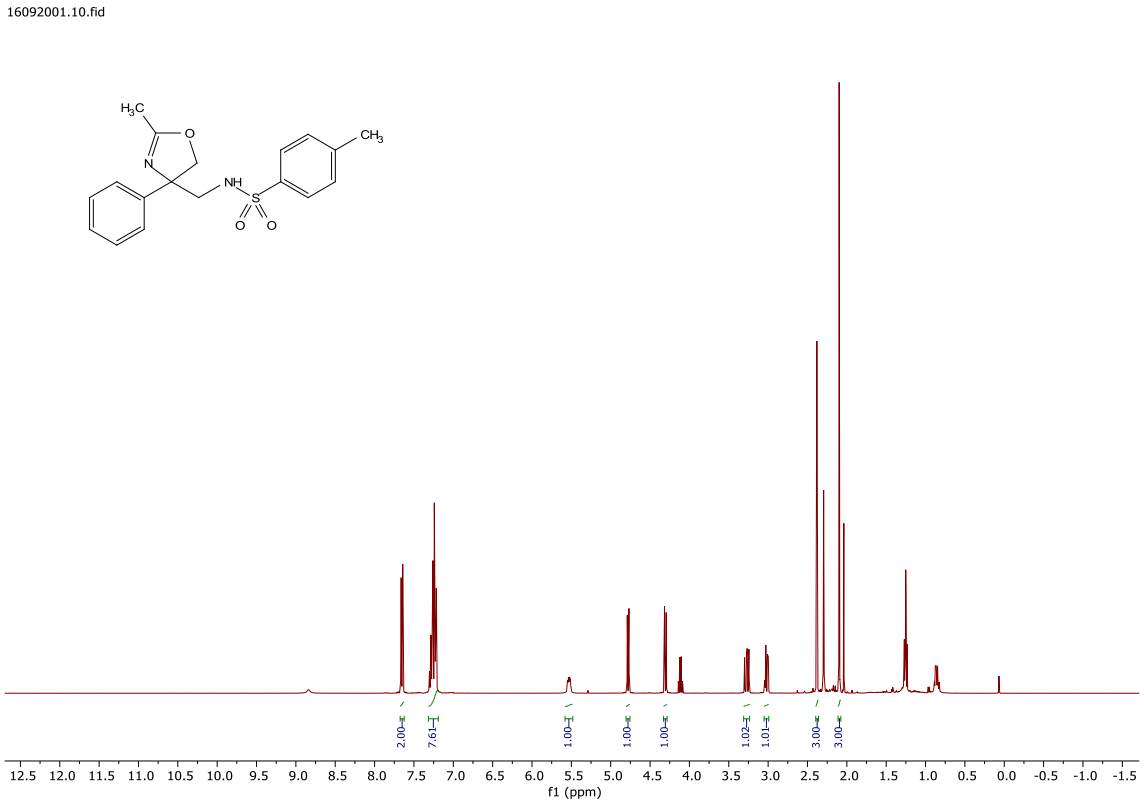
[5] W. Li, Y. Duan, M. Zhang, J. Cheng, C. Zhu, *Chem. Comm*. ***2016***, *48*, 7596−7599.

[6] S. Miyata T. Kumamoto T. Ishikawa, *Helvetica Chim*

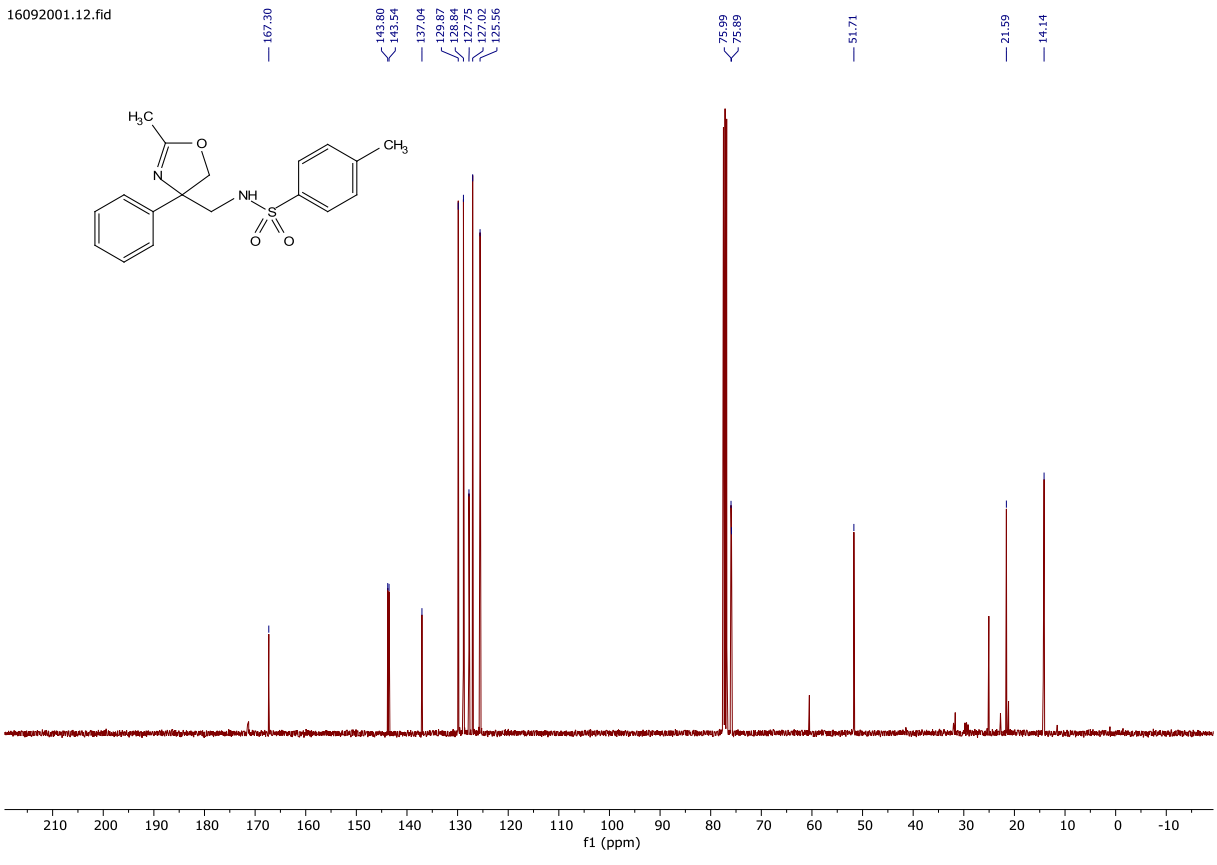
Chapter 2

A rearrangement of 3-hydroxyazetidines into 2-oxazolines.

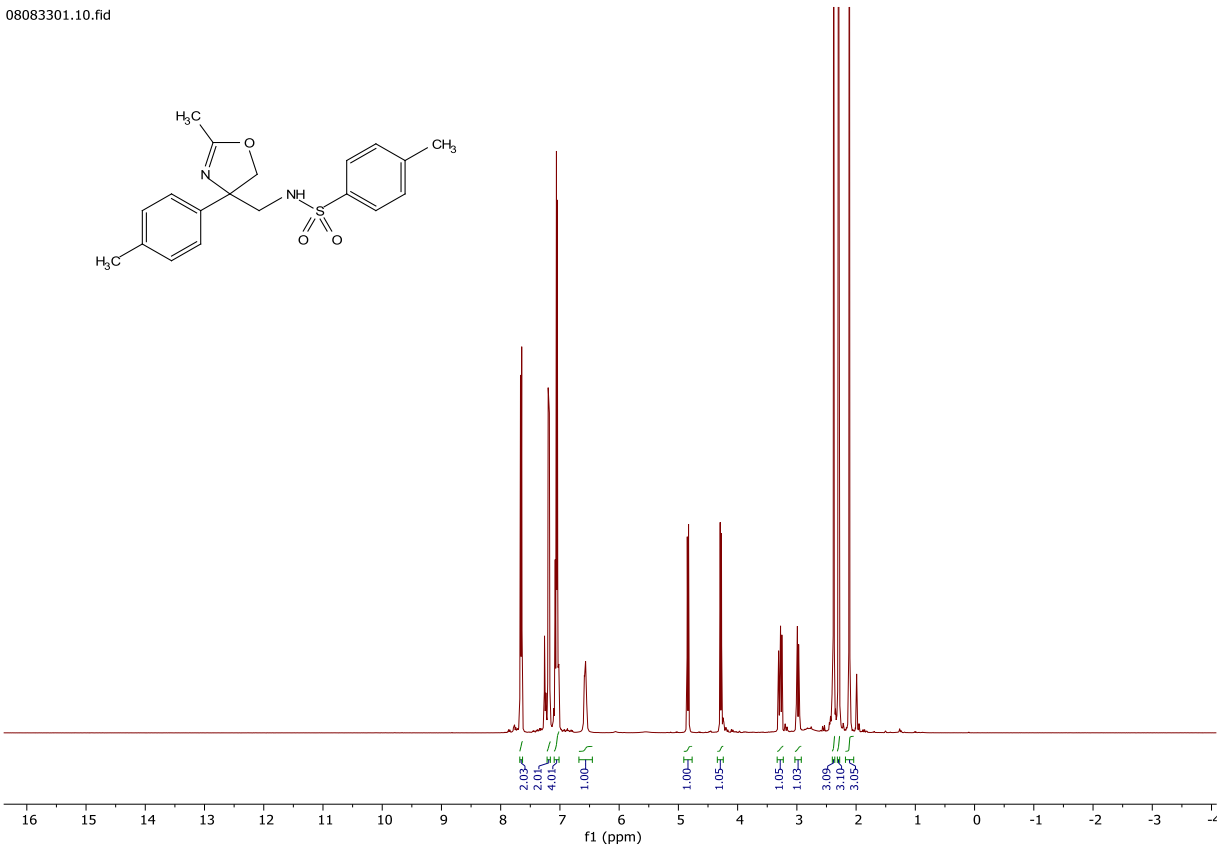
Compound 2-164 ^{1}H NMR (400 MHz, $CDCl_3$)



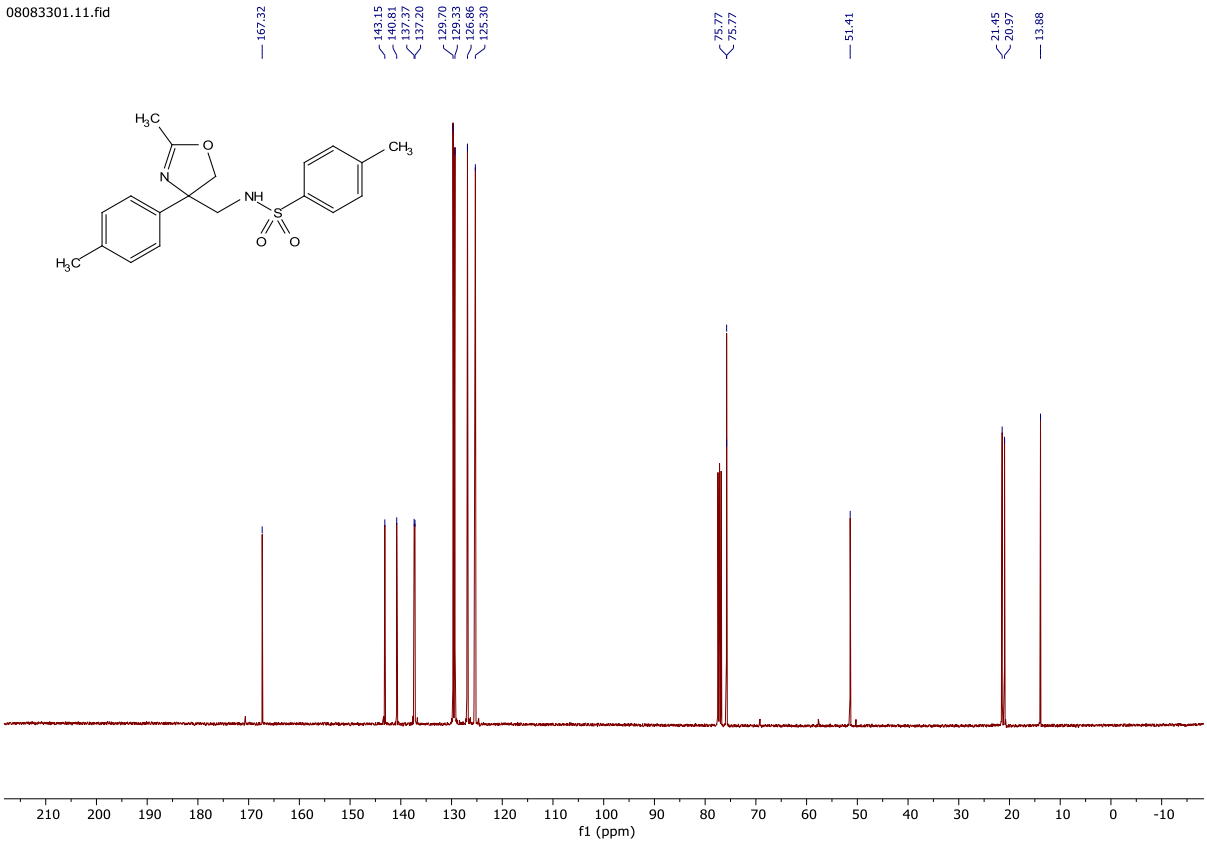
Compound **2-164** $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



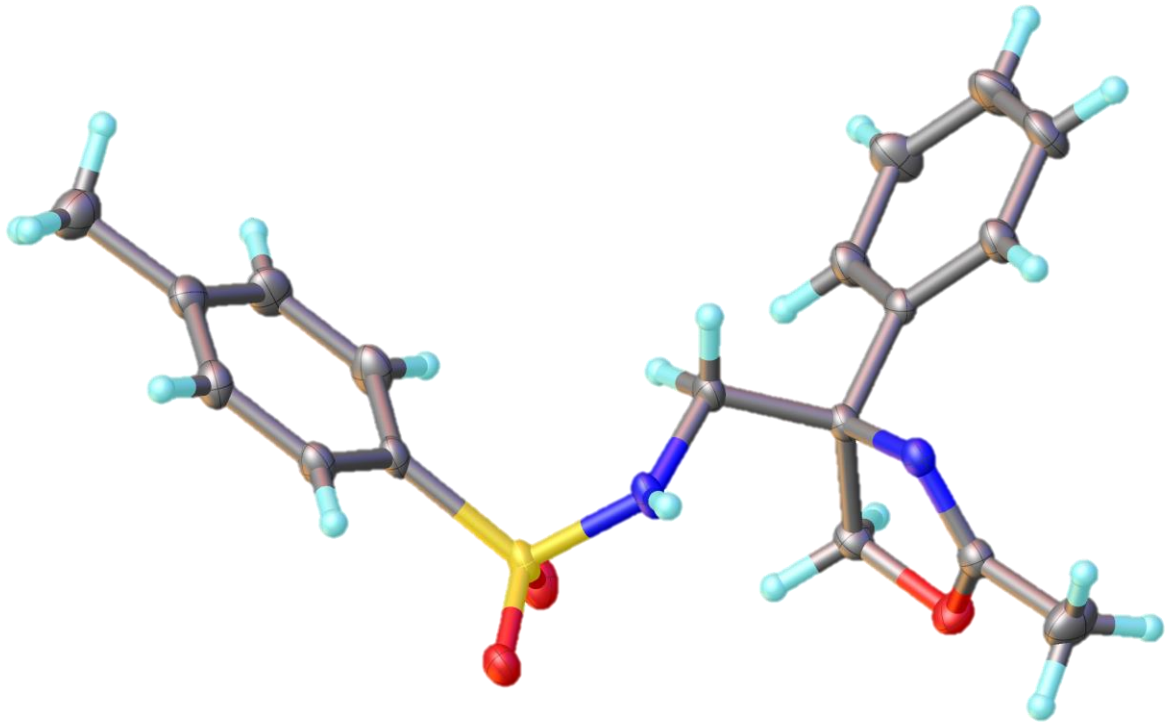
Compound 2-165 ^{1}H NMR (400 MHz, $CDCl_3$)



Compound **2-165** $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



Compound 2-164 X-ray structure



Atomic displacement ellipsoids are drawn at the 50% probability level.

Compound 4-2 was crystallised by solvent evaporation using a mixture Hexane: EtOAc

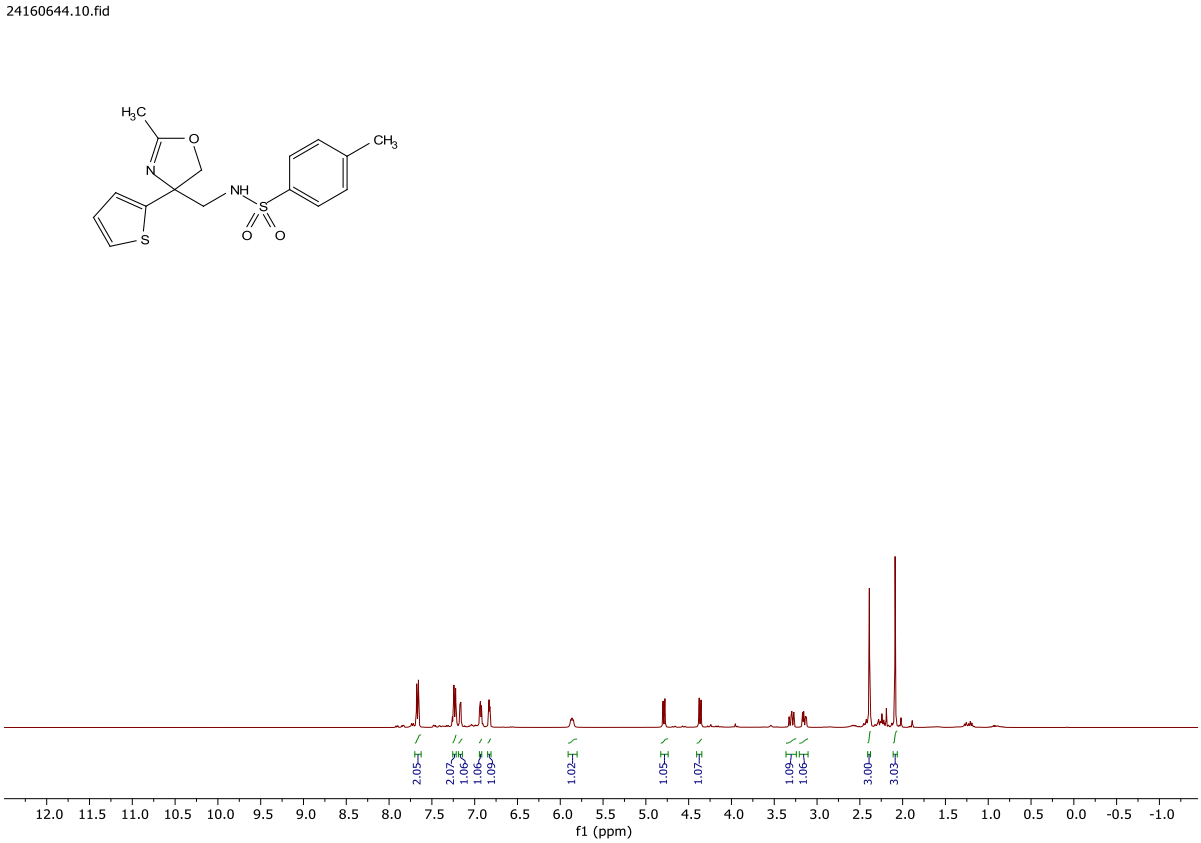
Experimental

Single crystals of $C_{25}H_{22}BrClN_2O_4S$ were A suitable crystal was selected on a D8V_Mo diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

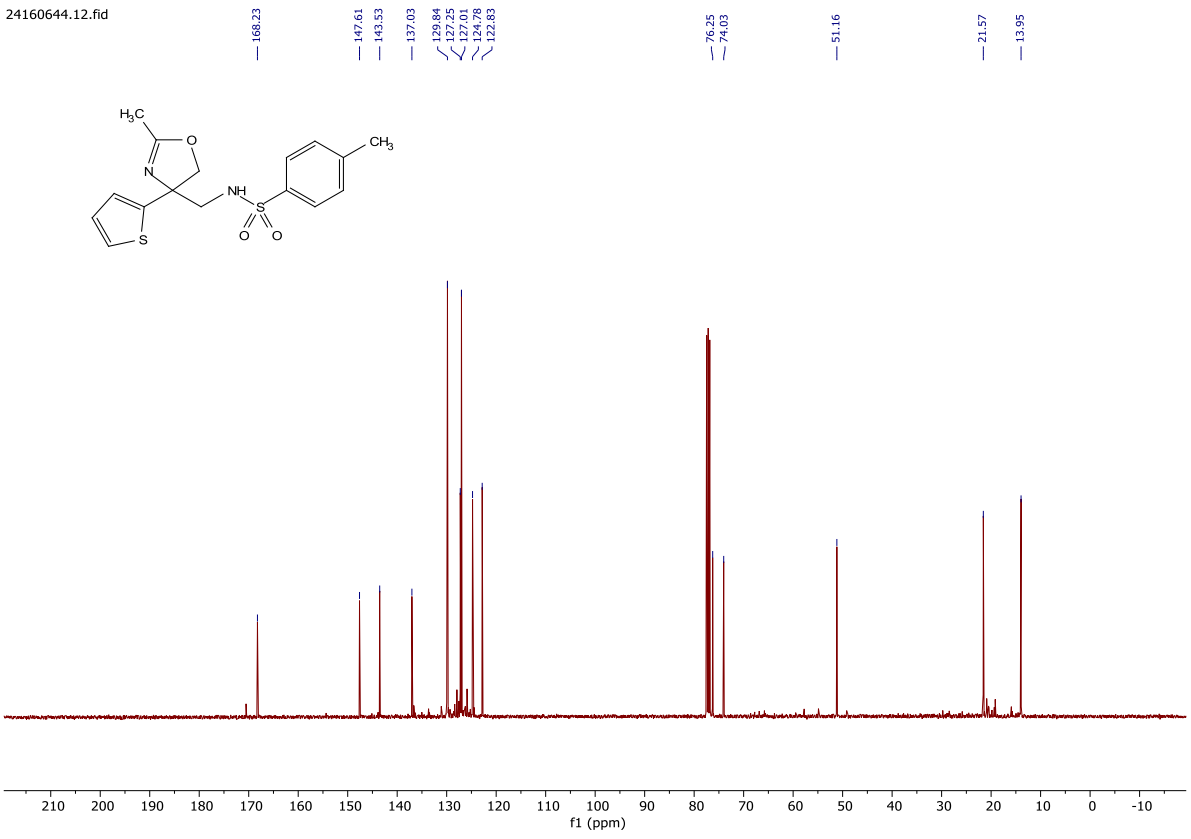
1) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2) Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
3) Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data for $C_{25}H_{22}BrClN_2O_4S$ (M =561.86 g/mol): triclinic, space group P-1 (no. 2), a = 8.9040(5) Å, b = 11.4226(7) Å, c = 11.9517(7) Å, α = 81.001(2)°, β = 89.408(2)°, γ = 77.106(2)°, V = 1169.95(12) Å^3, Z = 2, T = 120 K, μ(MoKα) = 1.997 mm^{-1}, *Dcalc* = 1.595 g/cm^3, 26308 reflections measured (4.648° ≤ 2Θ ≤ 60.274°), 6888 unique (R_{int} = 0.0395, R_{sigma} = 0.0415) which were used in all calculations. The final R_1 was 0.0374 (I > 2σ(I)) and wR_2 was 0.1019 (all data).

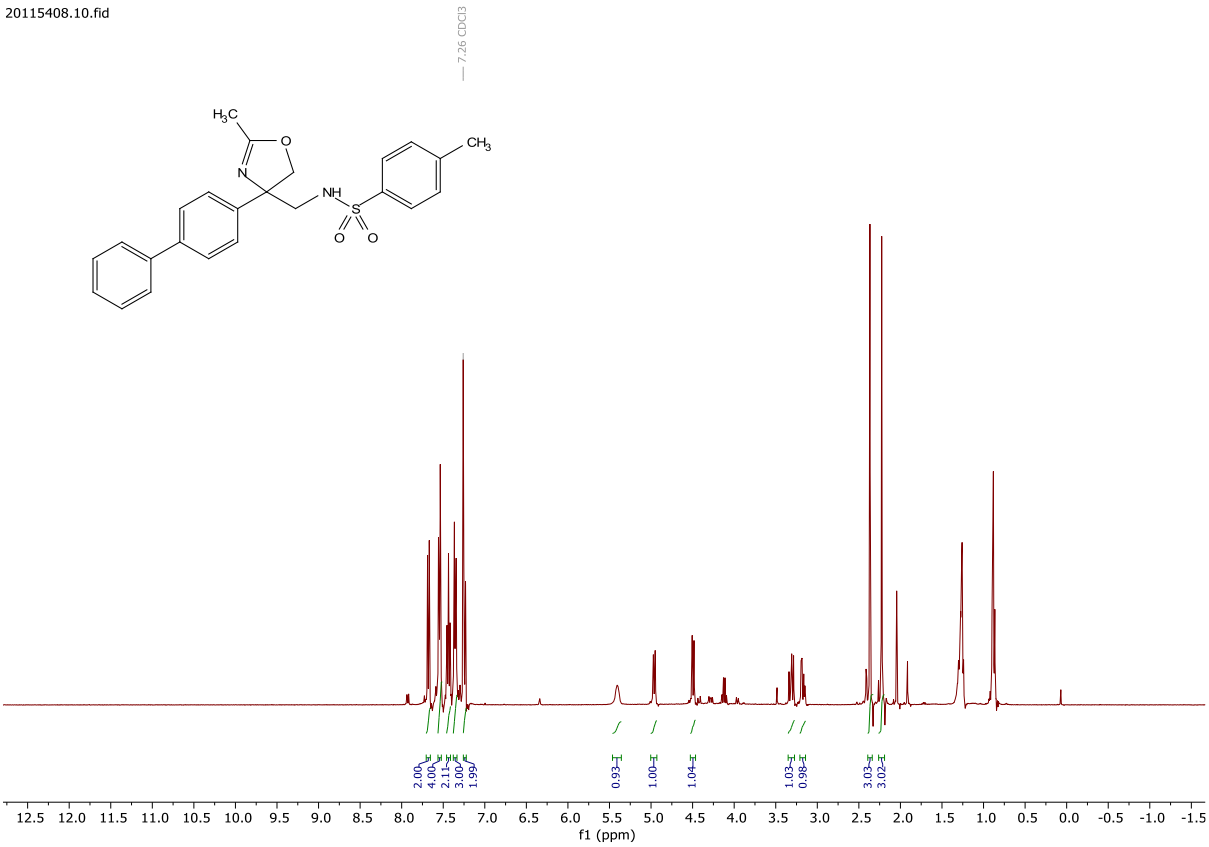
Compound 2-166 ^{1}H NMR (400 MHz, $CDCl_3$)



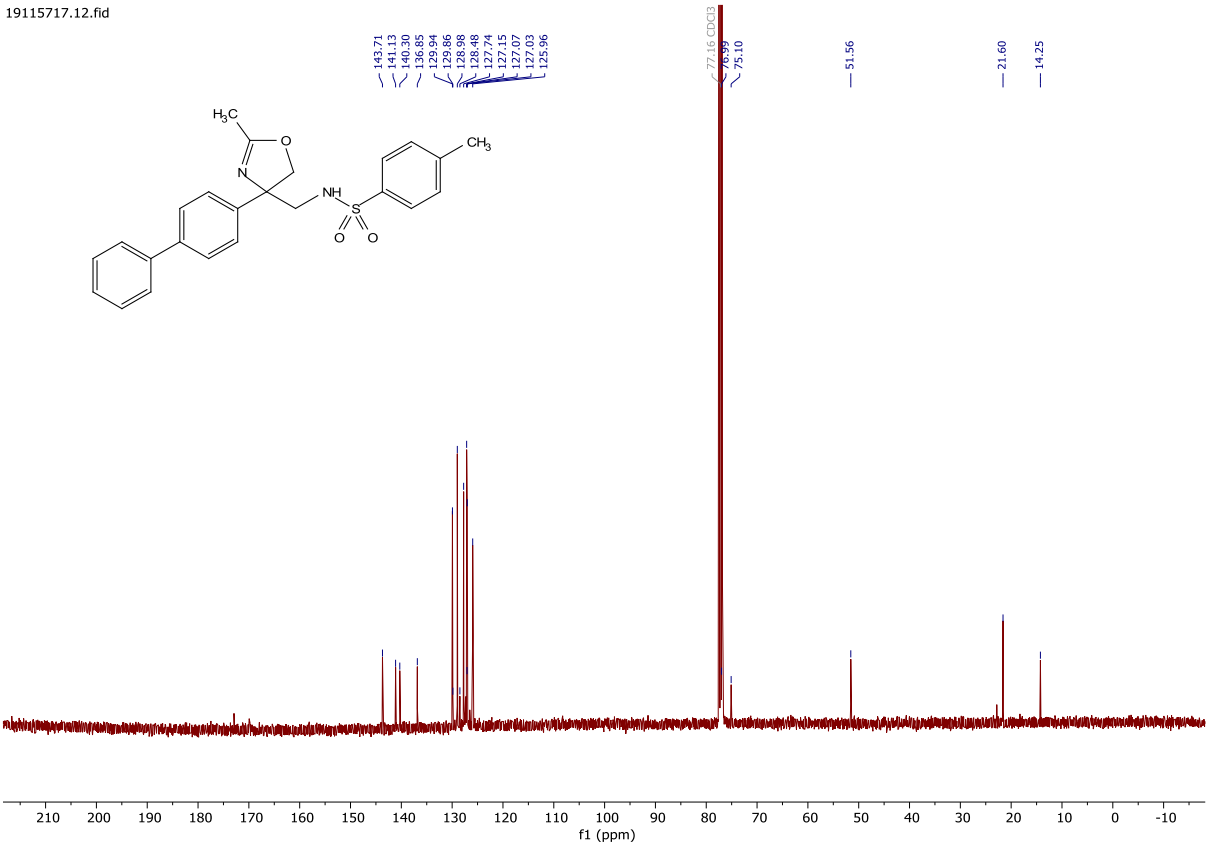
Compound **2-166** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



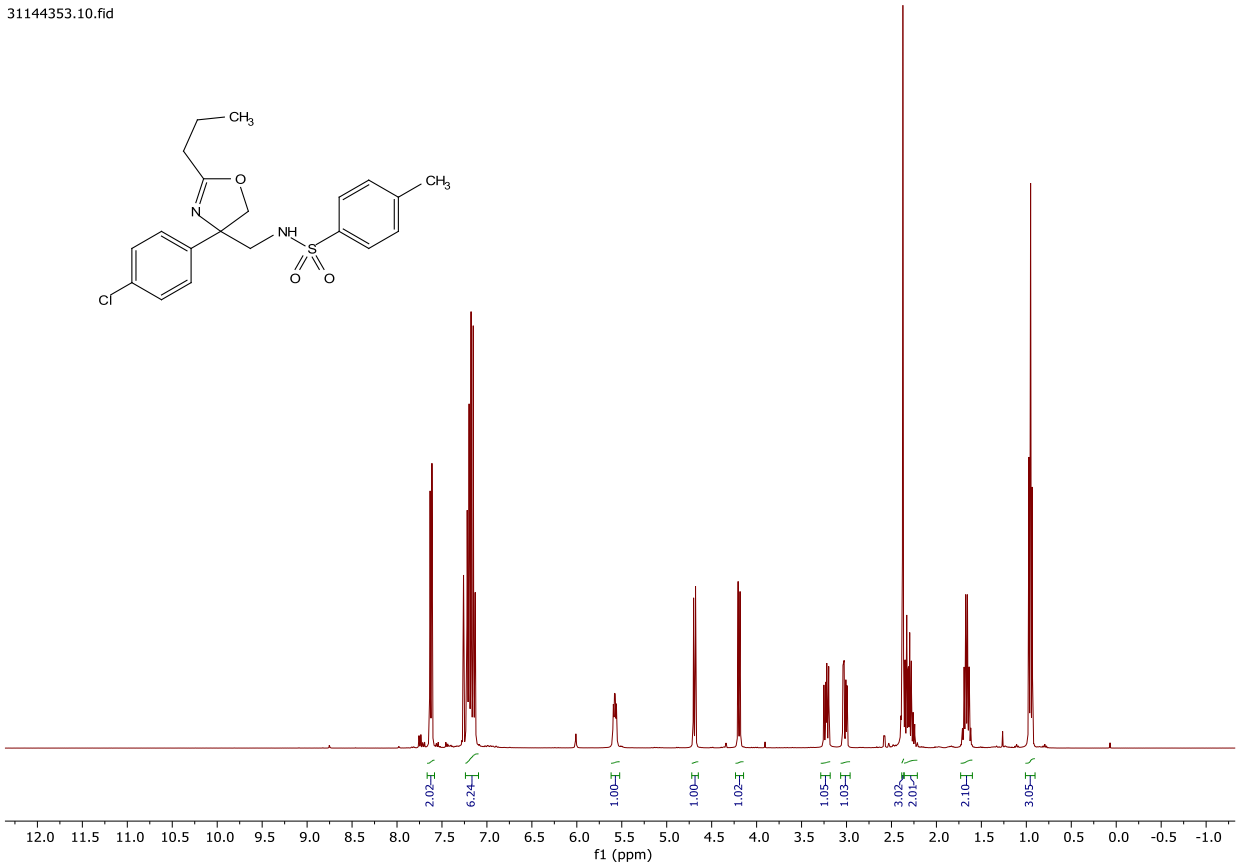
Compound 2-167 ^{1}H NMR (400 MHz, $CDCl_3$)



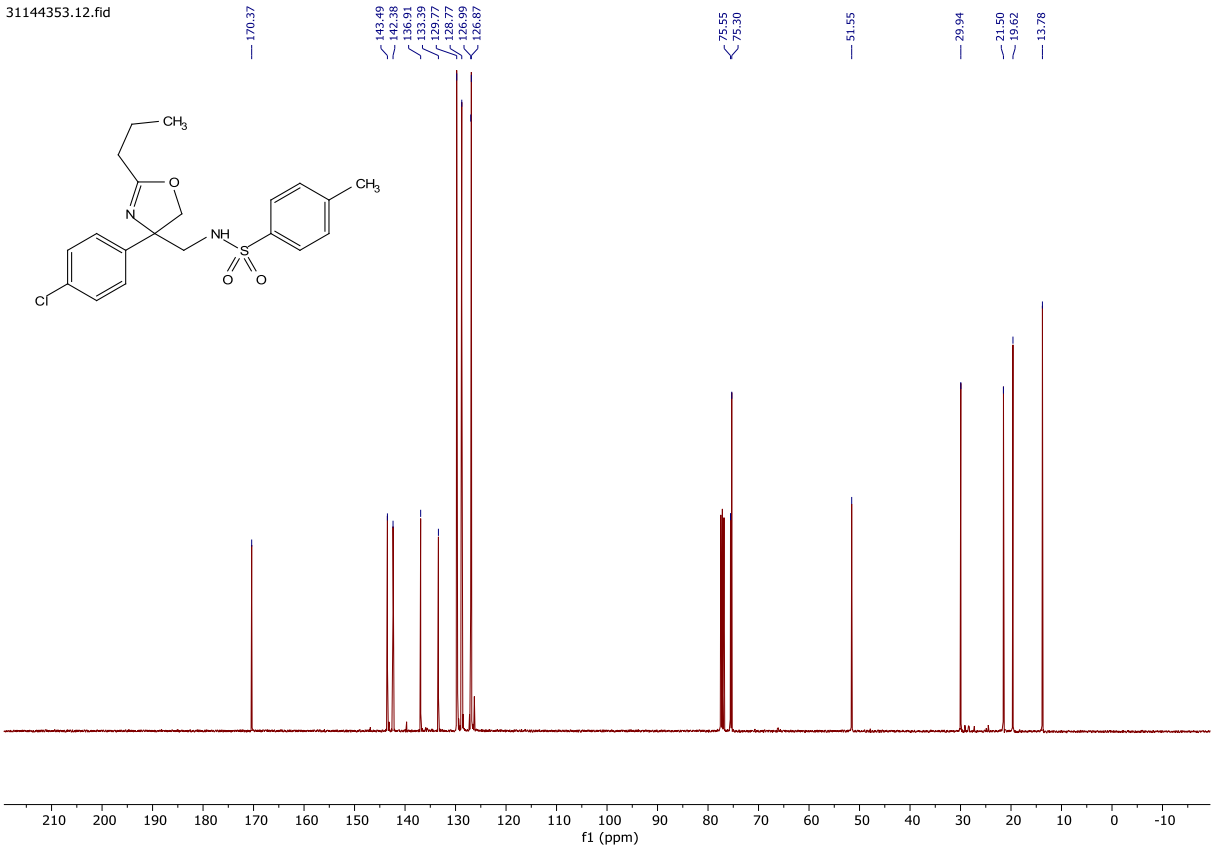
Compound **2-167** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



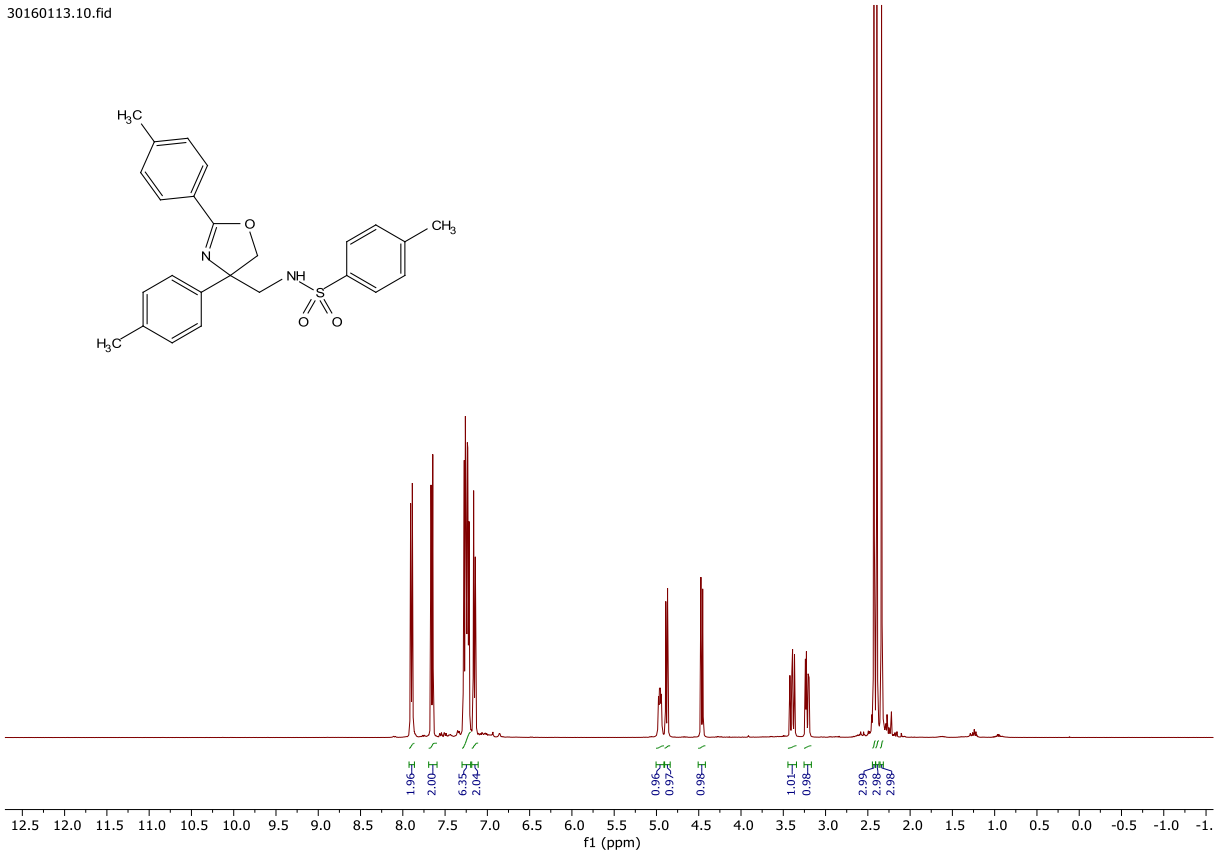
Compound 2-168 ^{1}H NMR (400 MHz, $CDCl_3$)



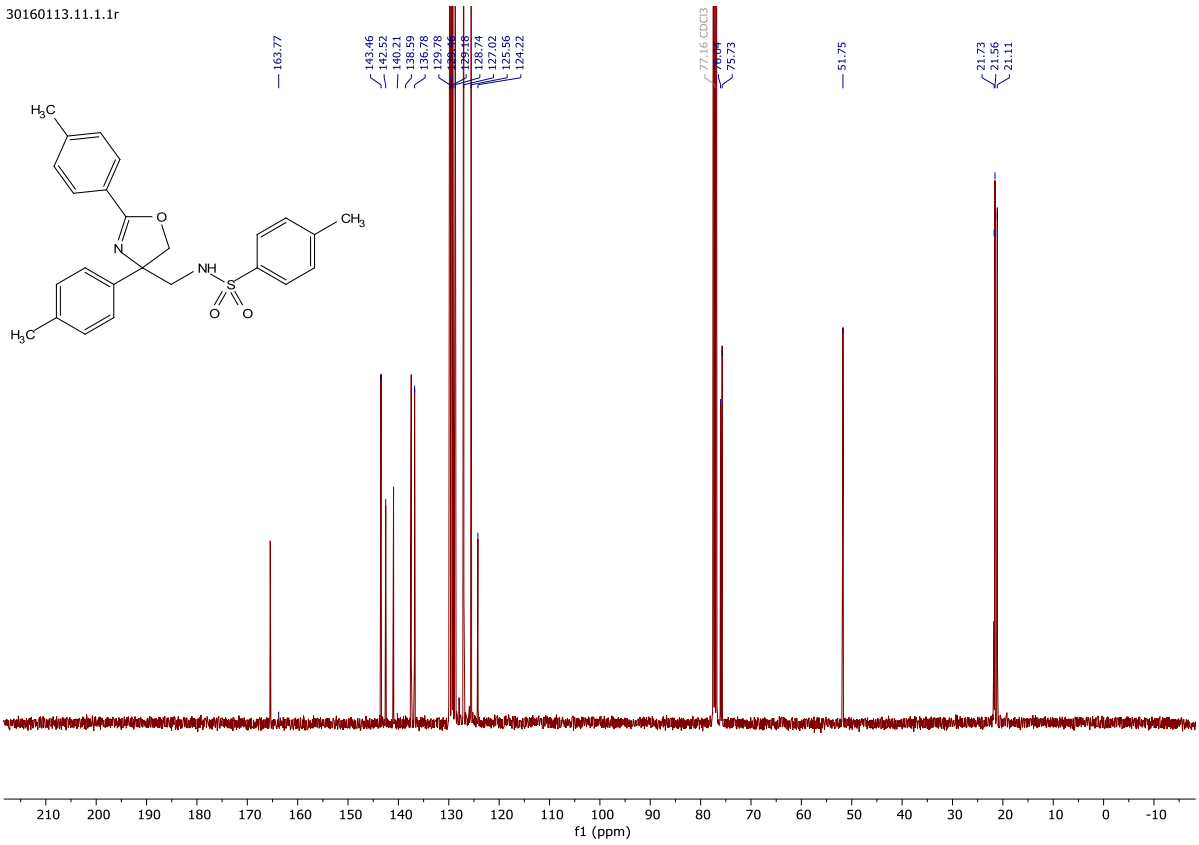
Compound **2-168** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



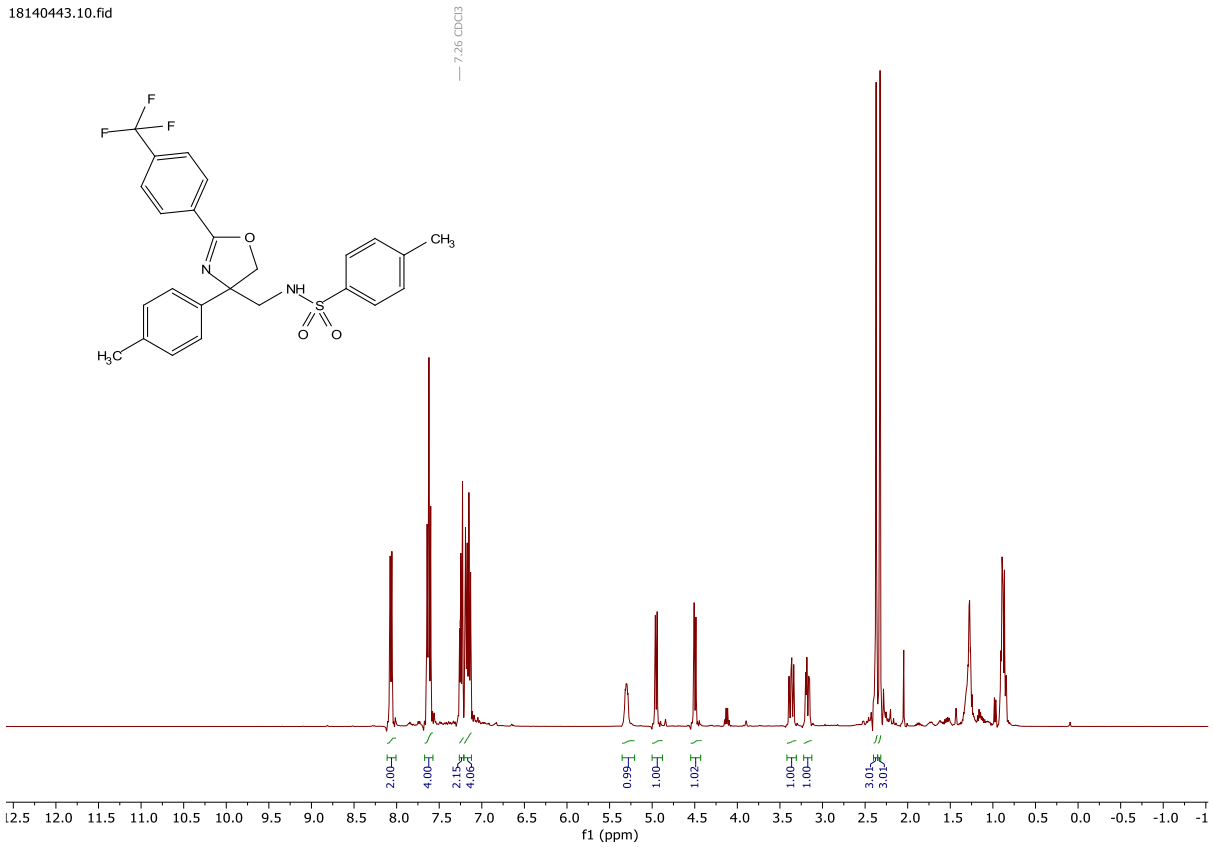
Compound 2-169 ^{1}H NMR (400 MHz, $CDCl_3$)



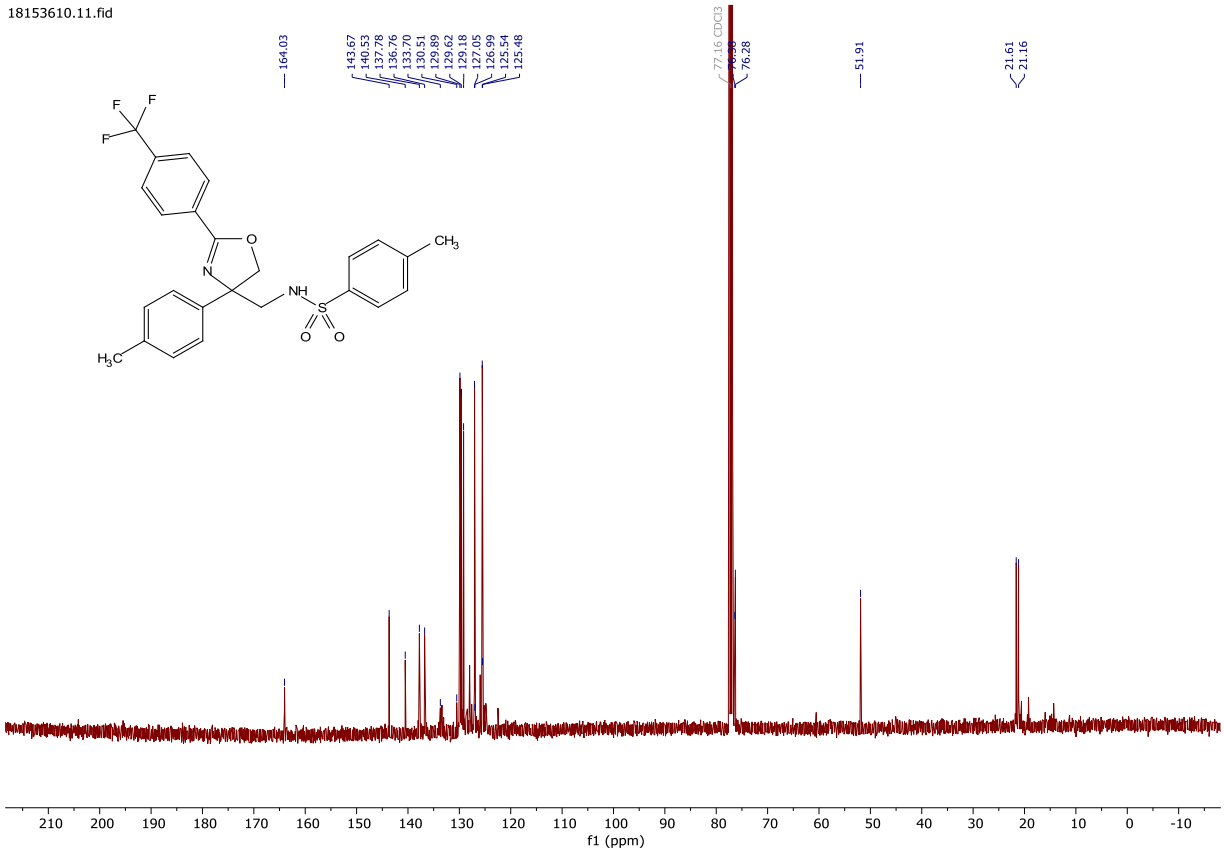
Compound **2-169** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



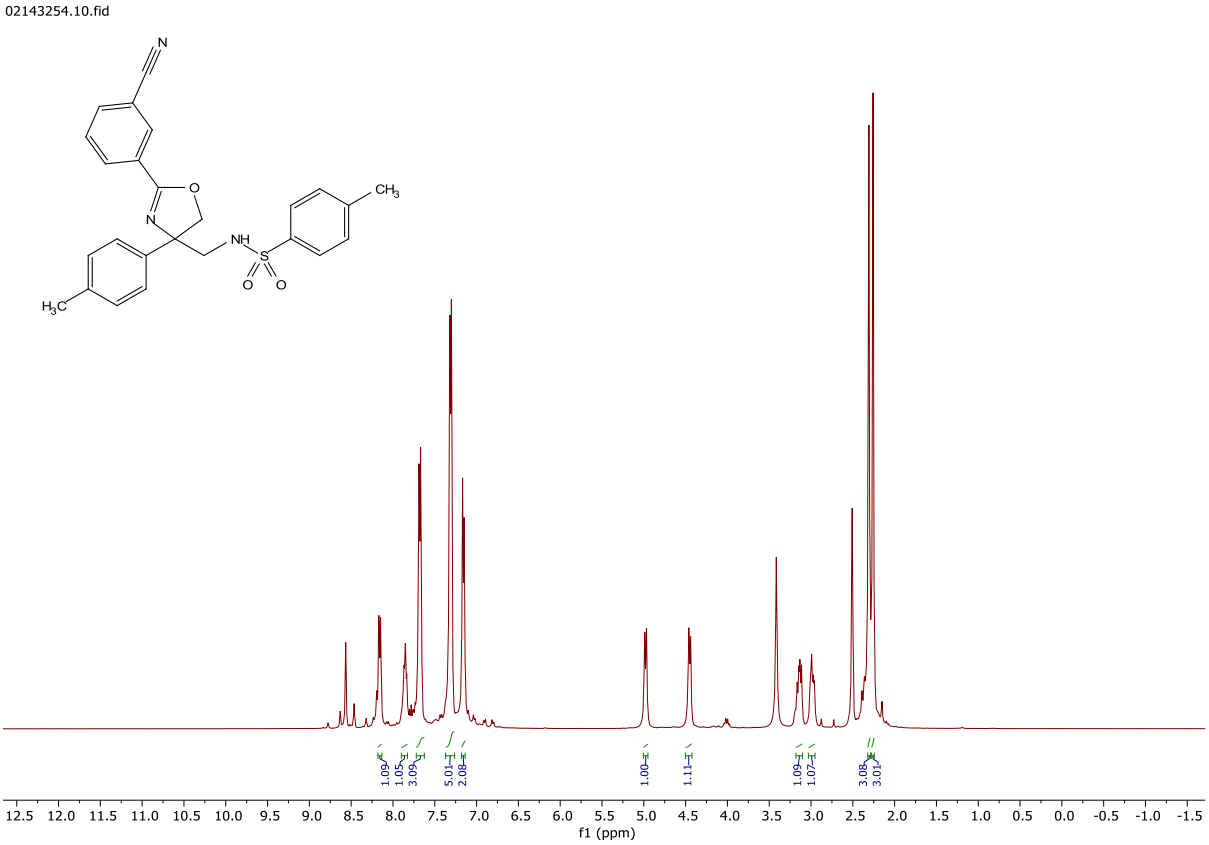
Compound 2-170 ^{1}H NMR (400 MHz, $CDCl_3$)



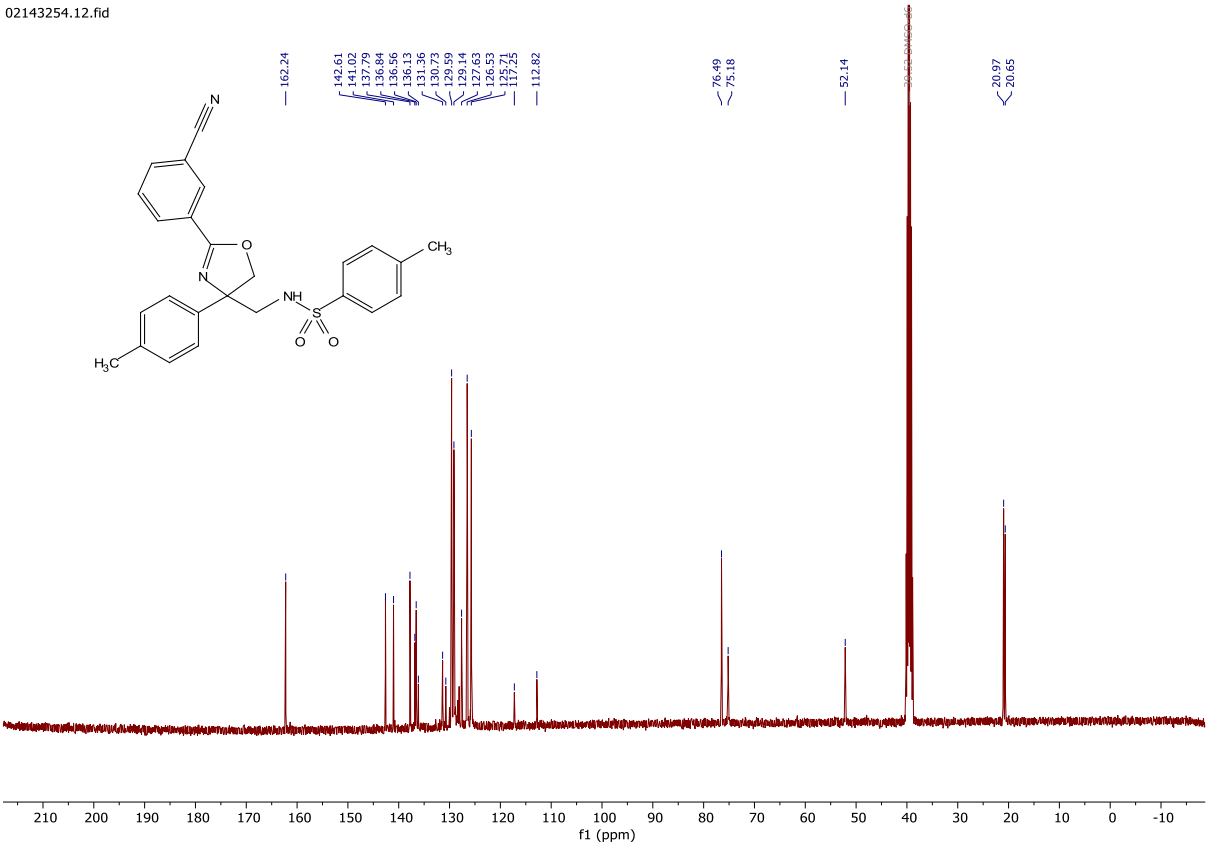
Compound 2-170 ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



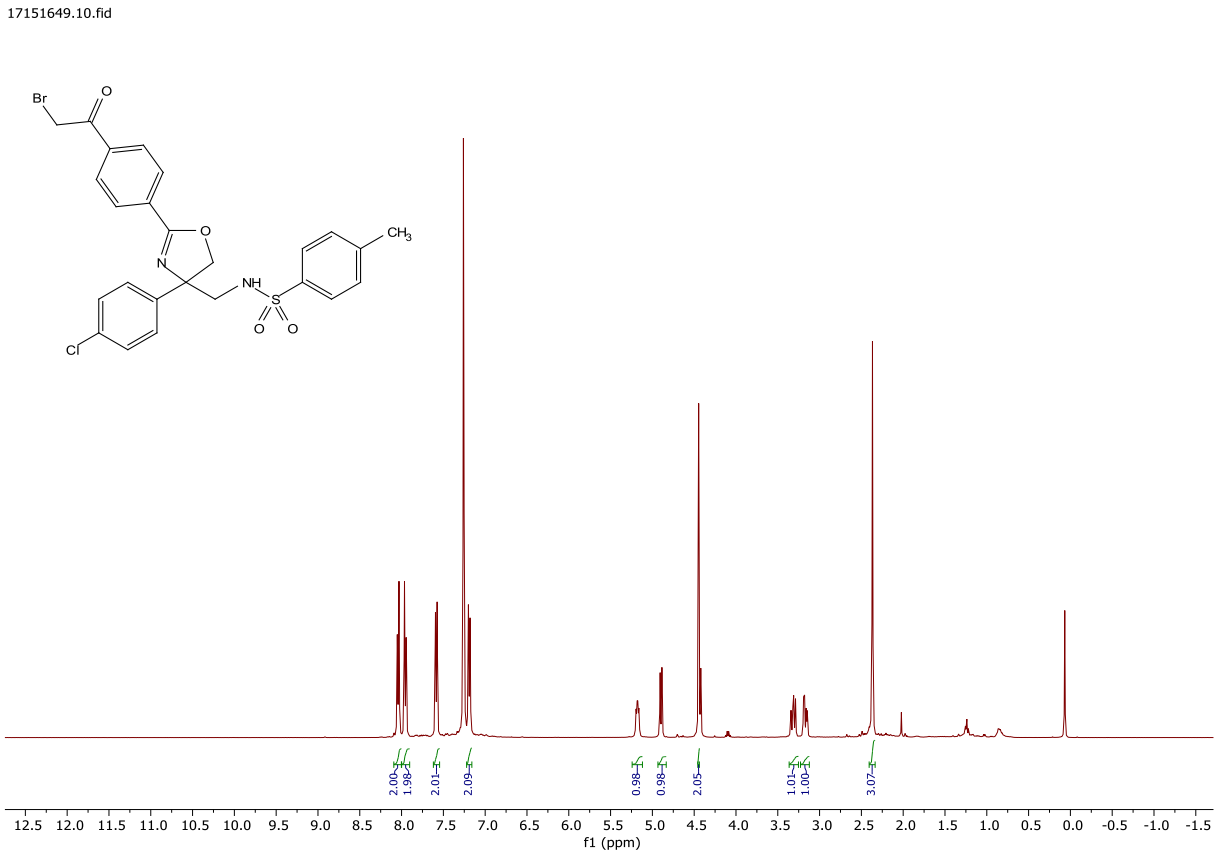
Compound 2-171 ^{1}H NMR (400 MHz, DMSO)



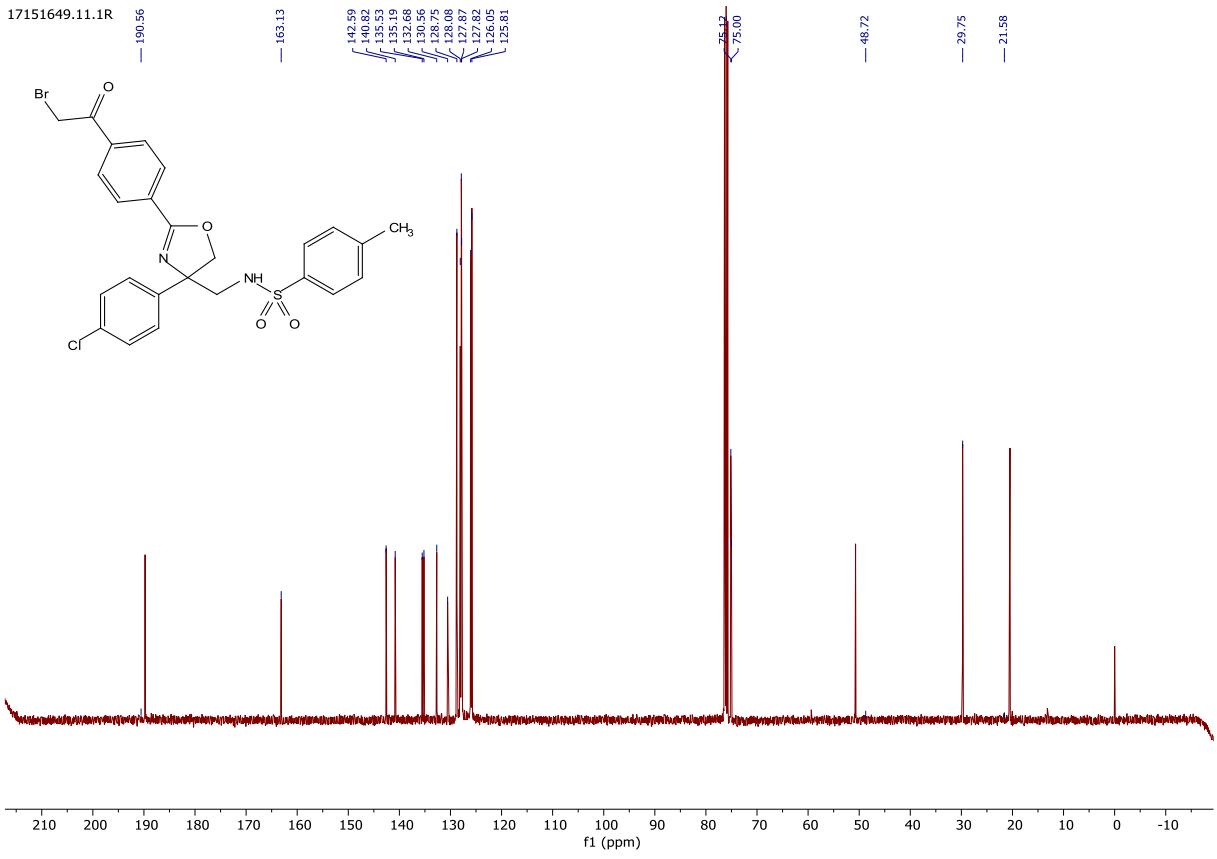
Compound **2-171** ^{13}C{^{1}H} NMR (101 MHz, DMSO)



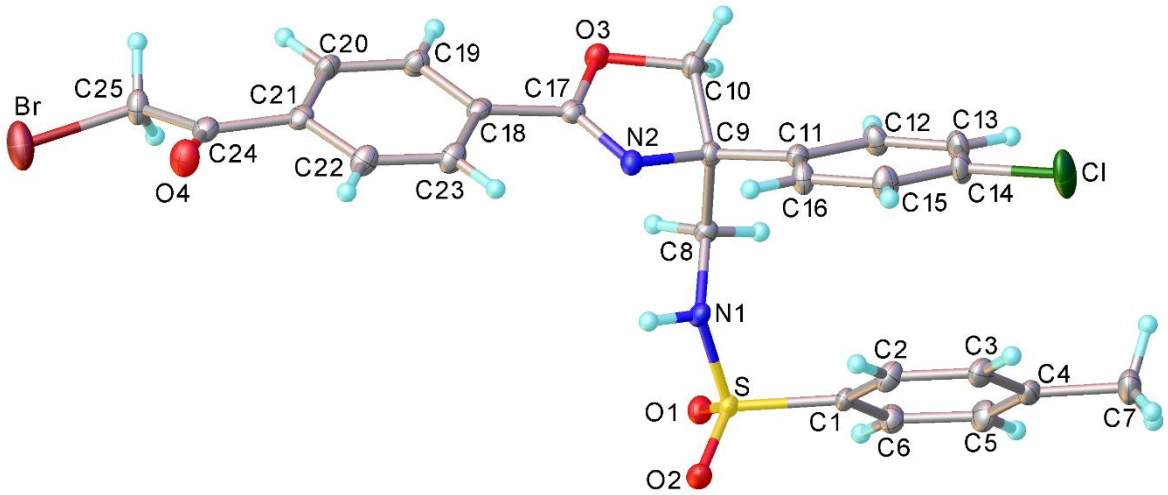
Compound 2-172 ^{1}H NMR (400 MHz, $CDCl_3$)



Compound **2-172** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



Compound 2-172 X-ray structure



Atomic displacement ellipsoids are drawn at the 50% probability level.

Compound 4-9 was crystallised by solvent evaporation using a mixture Hexane: EtOAc

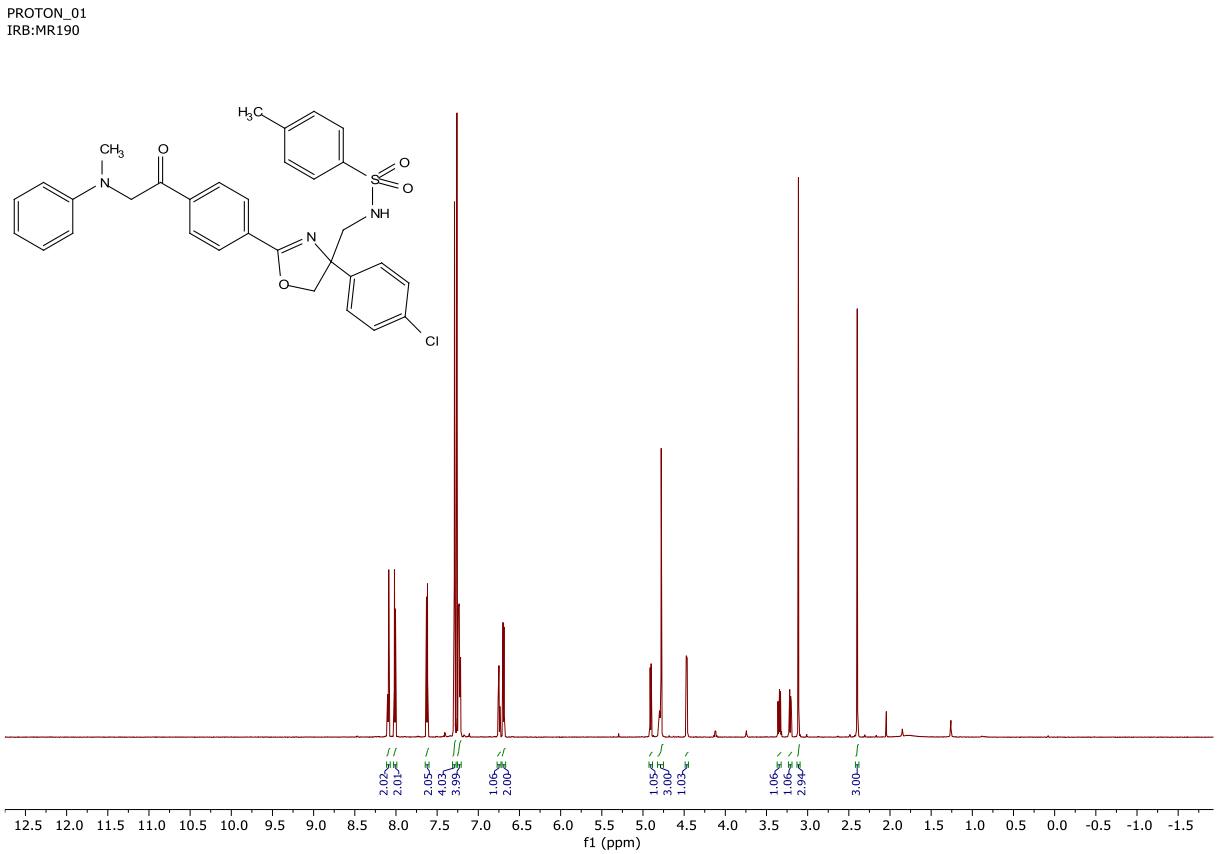
Experimental

Single crystals of $C_{25}H_{22}BrClN_2O_4S$ were A suitable crystal was selected on a D8V_Mo diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

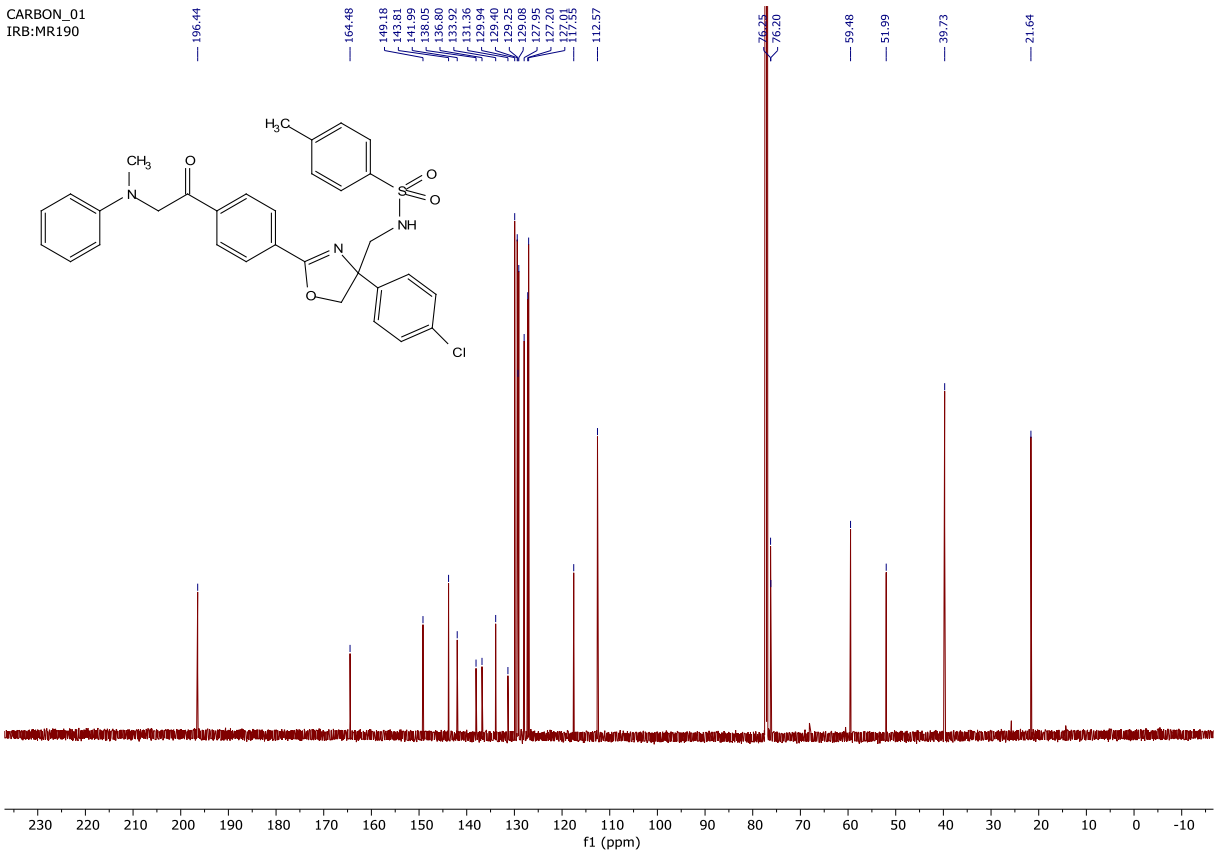
1) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2) Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
3) Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data for $C_{25}H_{22}BrClN_2O_4S$ (M =561.86 g/mol): triclinic, space group P-1 (no. 2), a = 8.9040(5) Å, b = 11.4226(7) Å, c = 11.9517(7) Å, α = 81.001(2)°, β = 89.408(2)°, γ = 77.106(2)°, V = 1169.95(12) Å^3, Z = 2, T = 120 K, μ(MoKα) = 1.997 mm^{-1}, *Dcalc* = 1.595 g/cm^3, 26308 reflections measured (4.648° ≤ 2Θ ≤ 60.274°), 6888 unique (R_{int} = 0.0395, R_{sigma} = 0.0415) which were used in all calculations. The final R_1 was 0.0374 (I > 2σ(I)) and wR_2 was 0.1019 (all data).

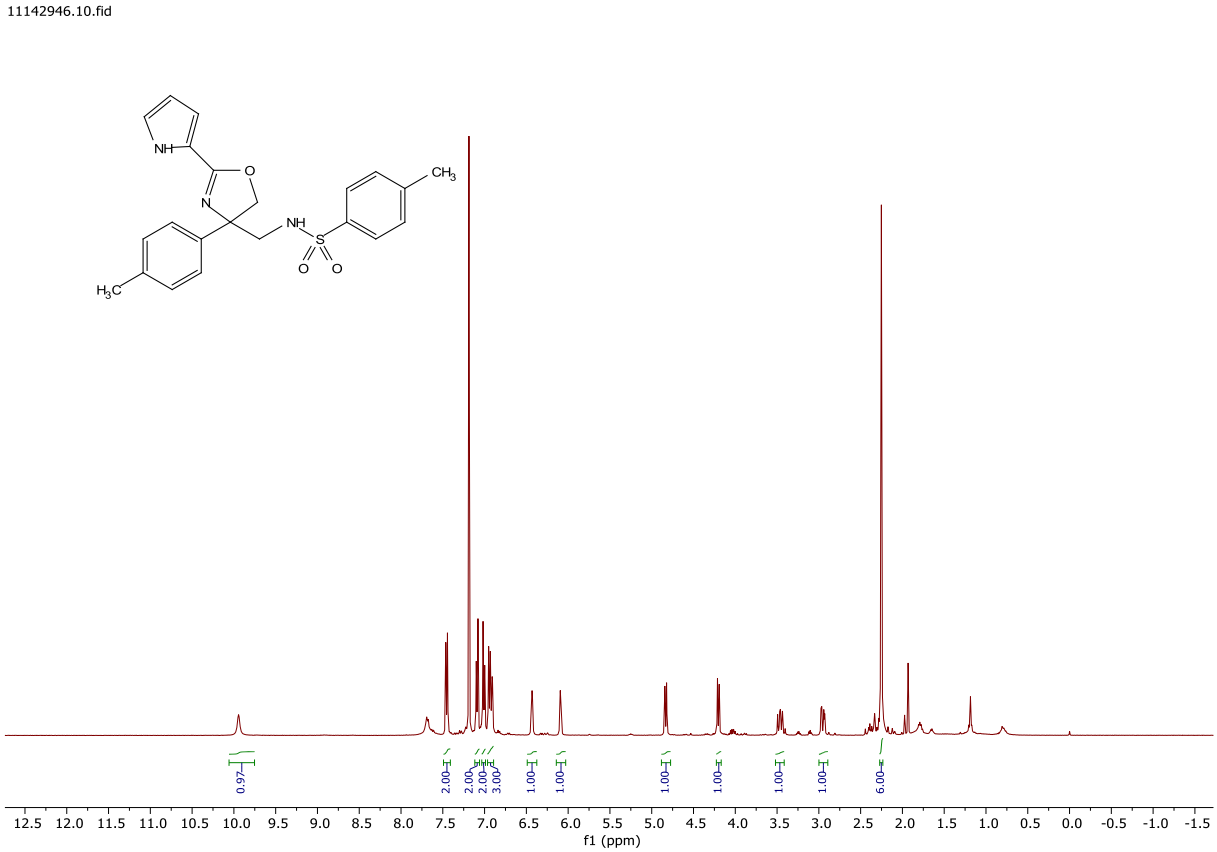
Compound 2-173 ^{1}H NMR (400 MHz, $CDCl_3$)



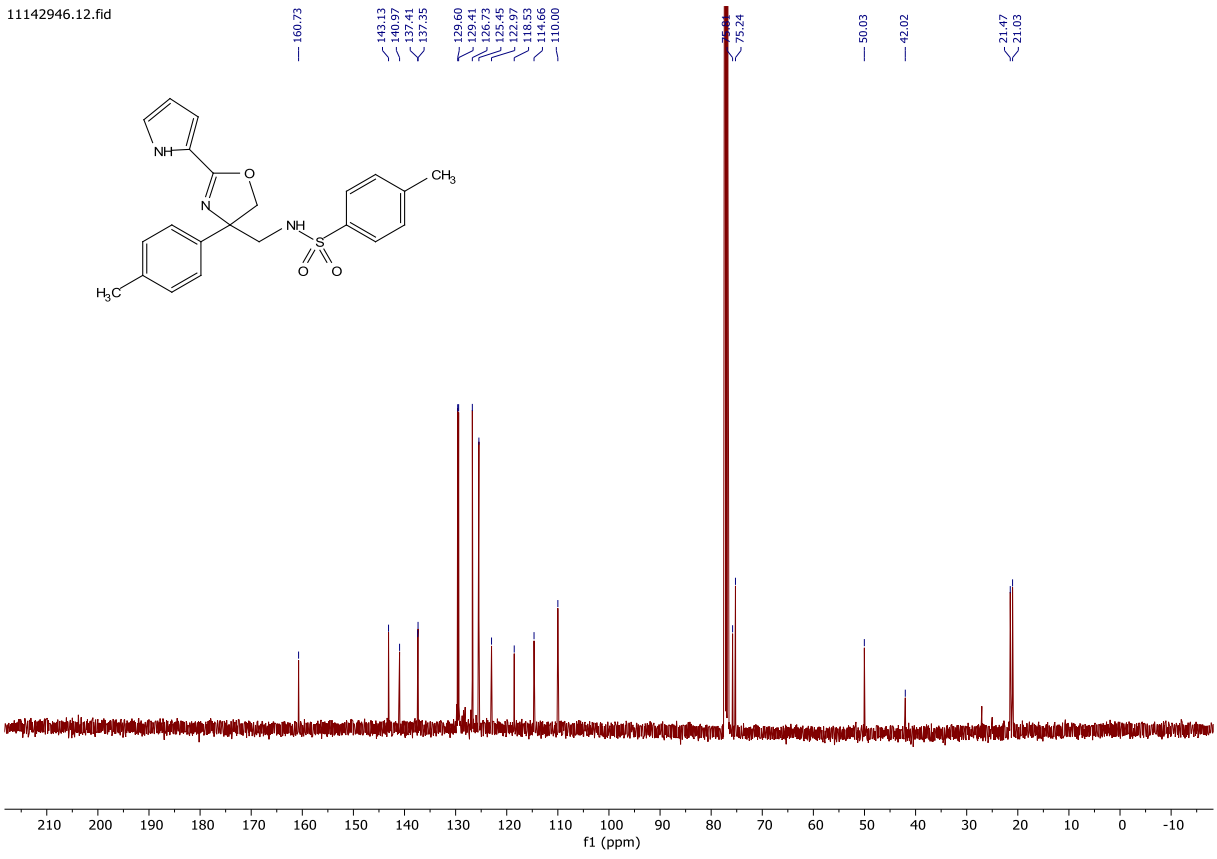
Compound **2-173** $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



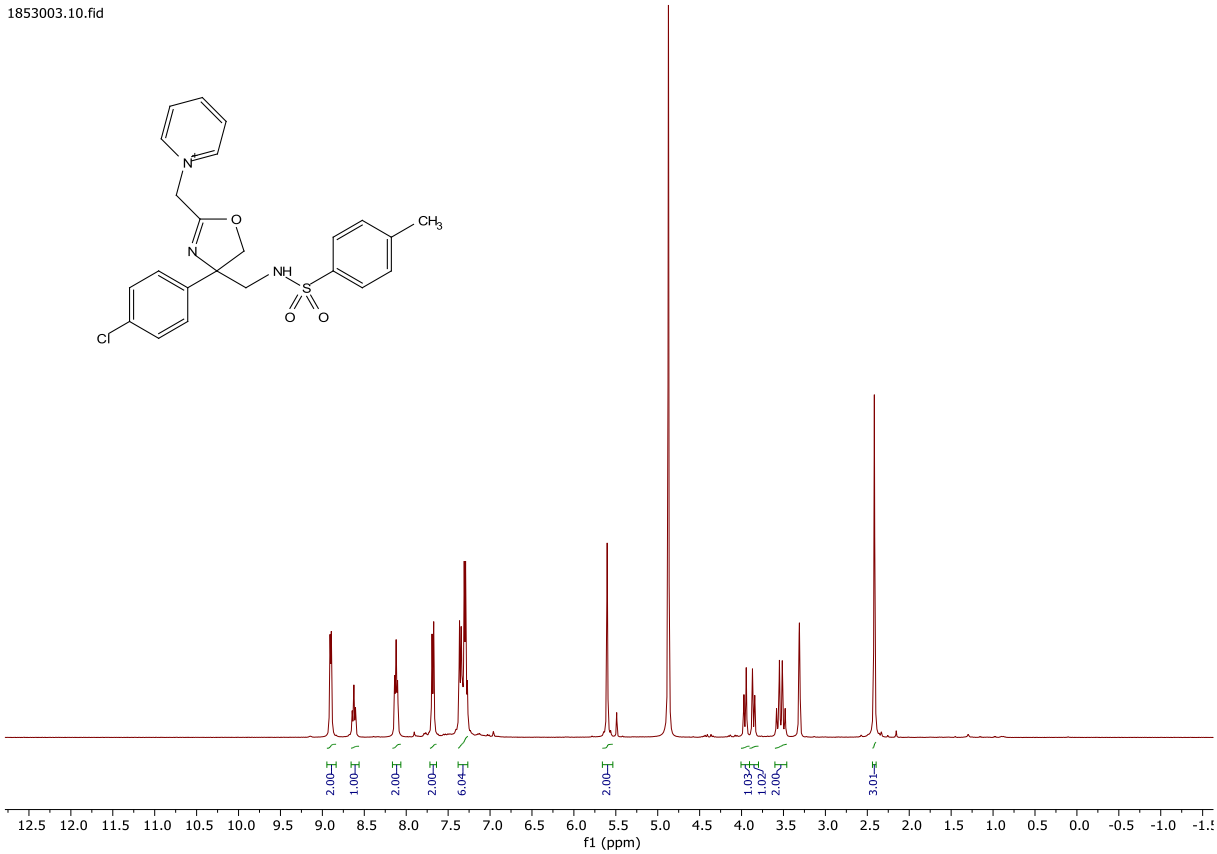
Compound 2-174 ^{1}H NMR (400 MHz, $CDCl_3$)



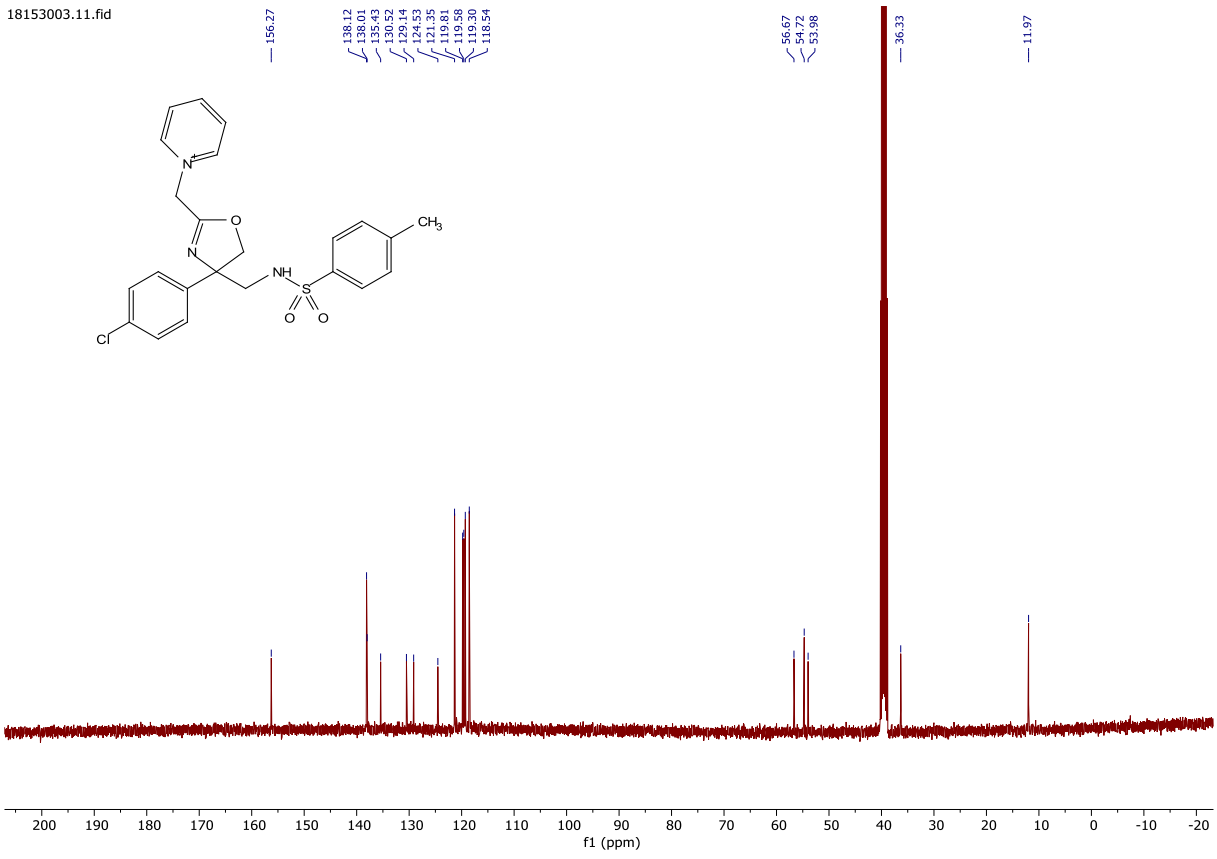
Compound **2-174** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



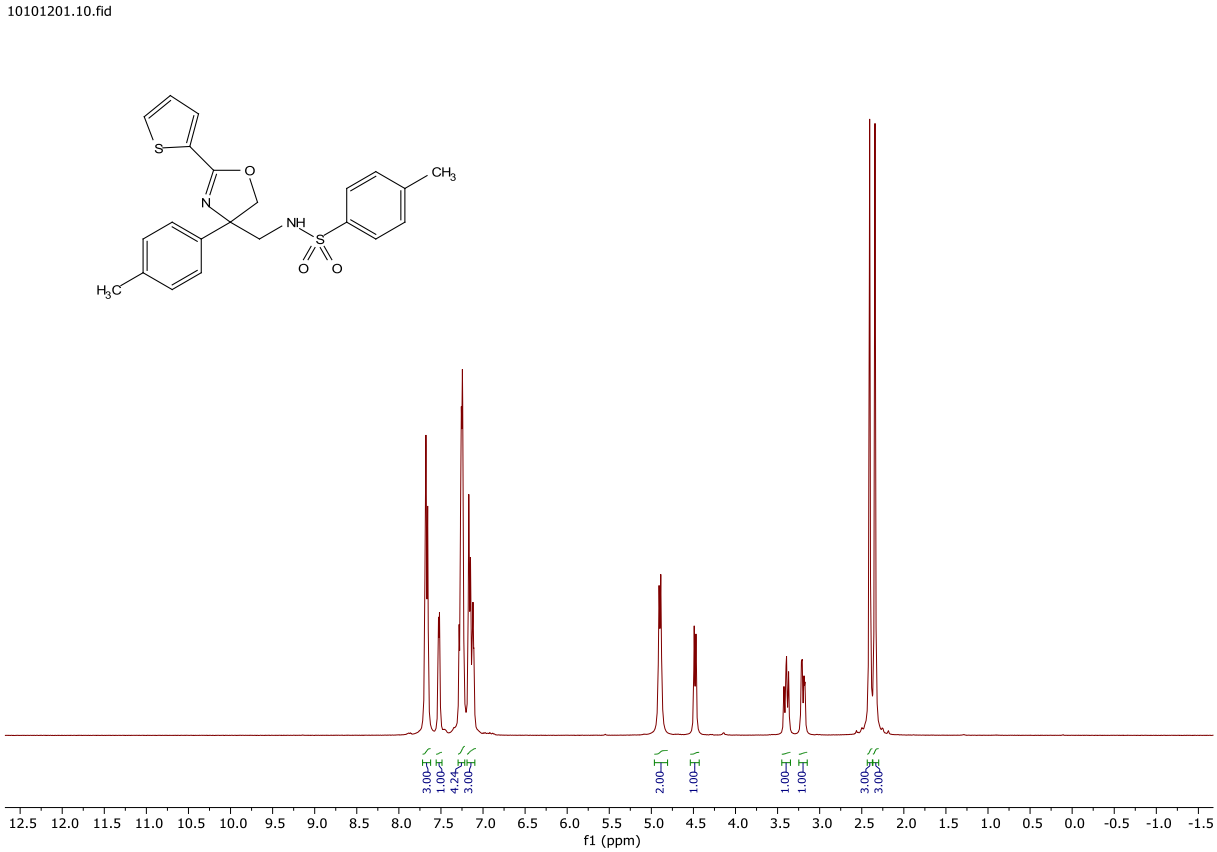
Compound 2-175 ^{1}H NMR (400 MHz, CD_3OD)



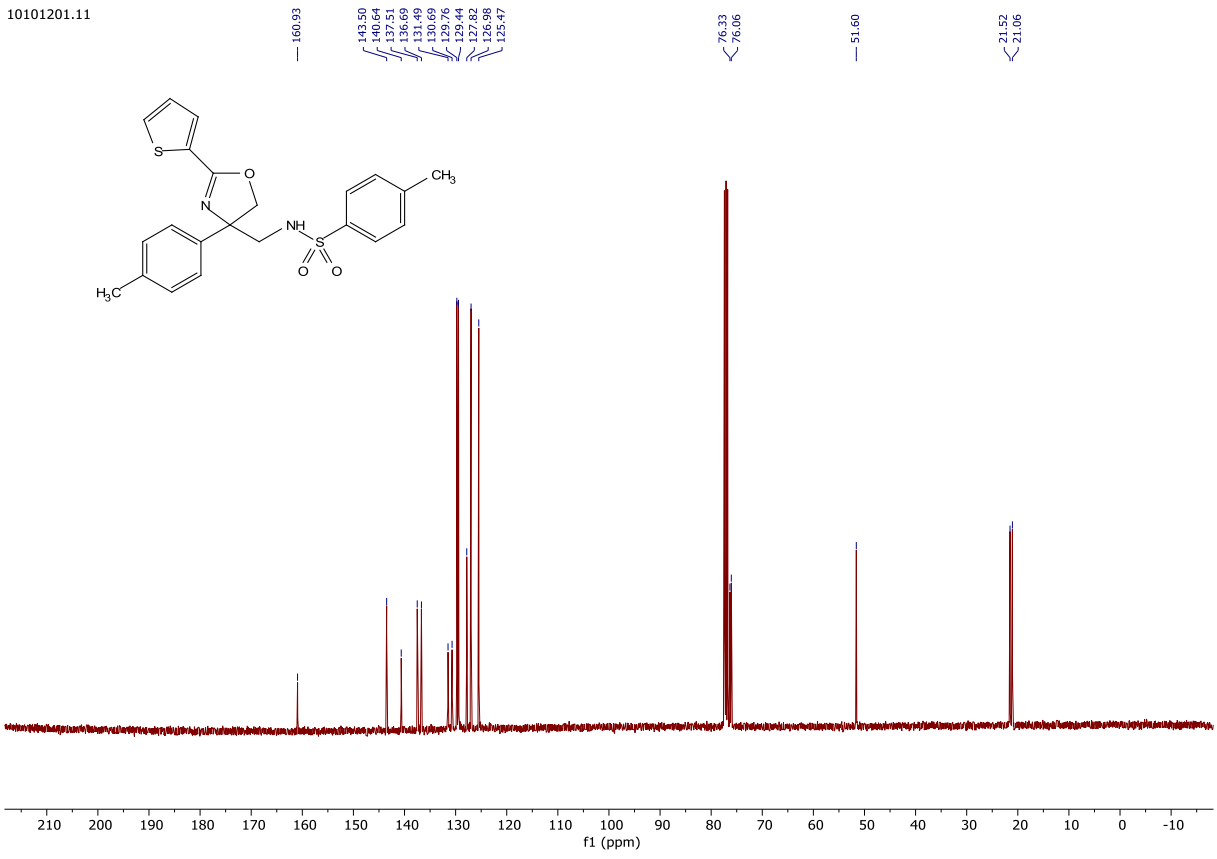
Compound **2-175** $^{13}C\{^{1}H\}$ NMR (101 MHz, CD_3OD)



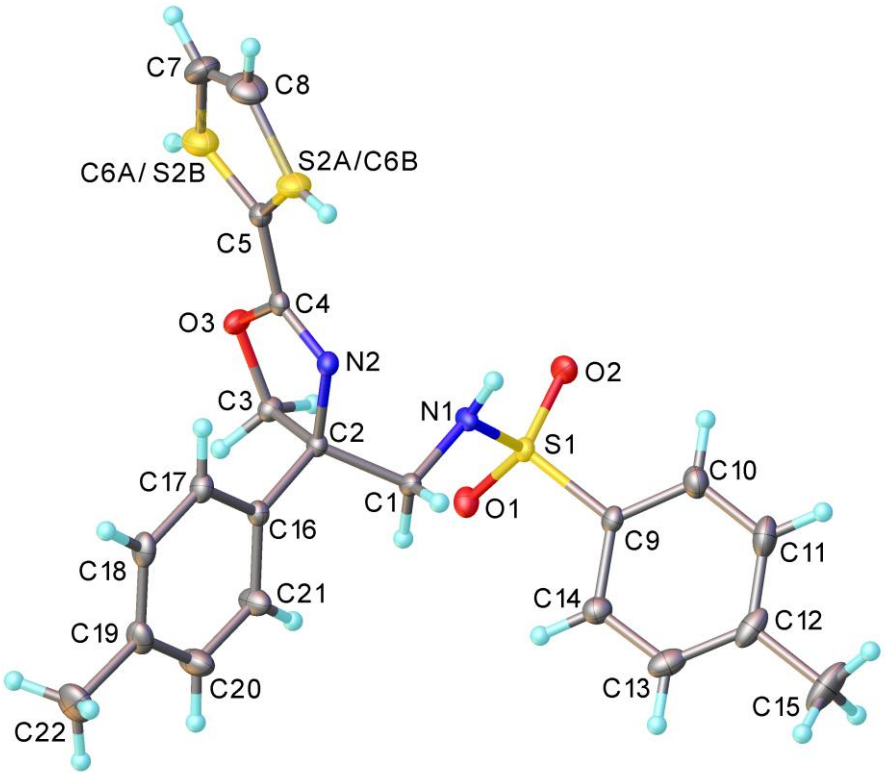
Compound 2-176 ^{1}H NMR (400 MHz, $CDCl_3$)



Compound **2-176** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



Compound 2-176 X-ray structure



Atomic displacement ellipsoids are drawn at the 50% probability level.

Compound 4-13 was crystallised by solvent evaporation using a mixture Hexane: EtOAc

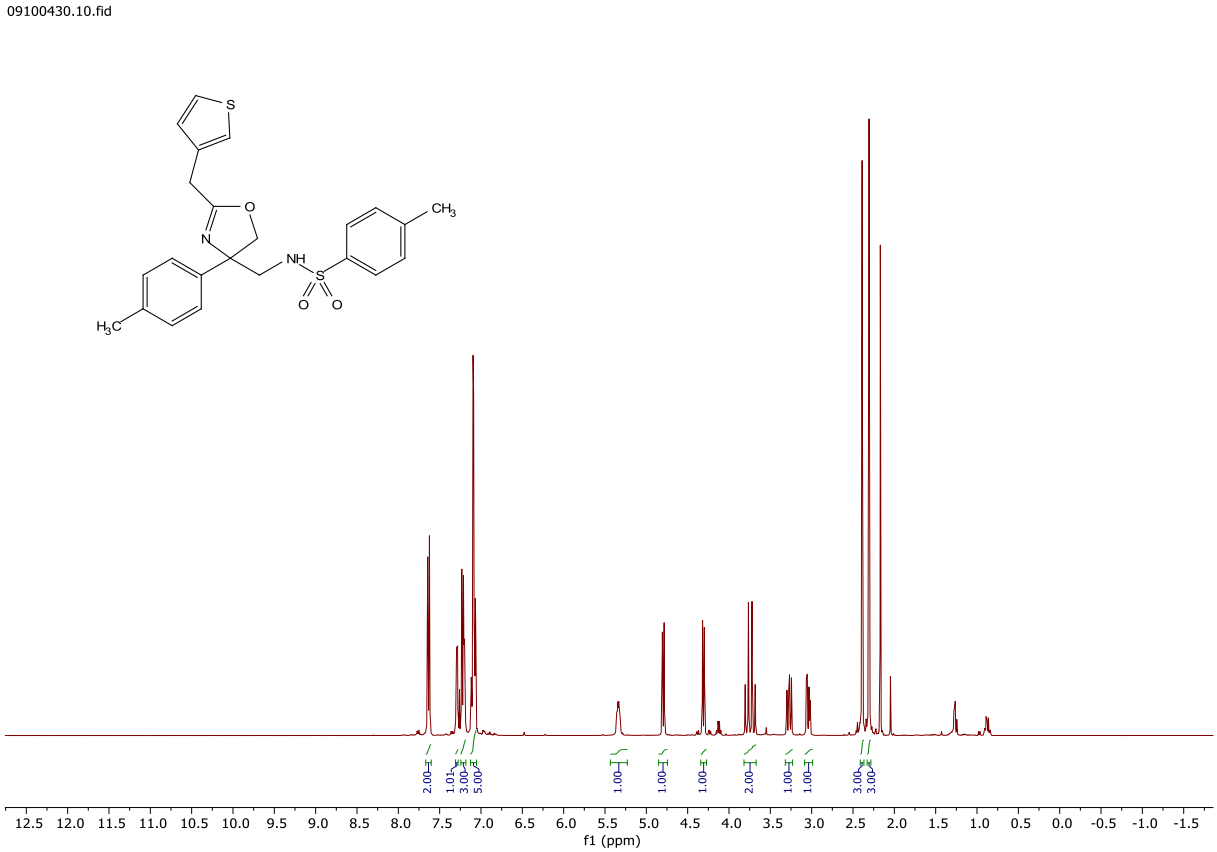
Experimental

Single crystals of $C_{23}H_{22}Cl_3DN_2O_3S$ were A suitable crystal was selected on a D8V_Mo diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

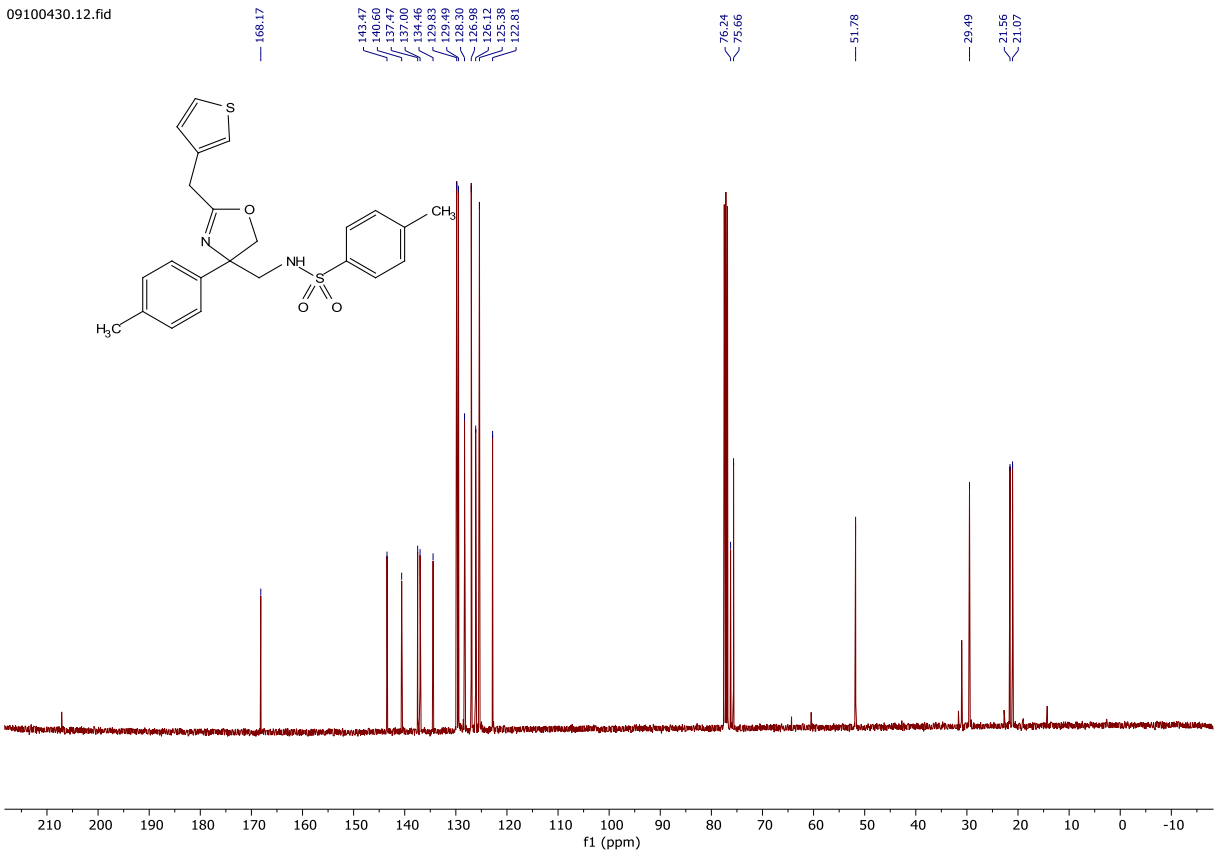
4) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
5) Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
6) Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data for $C_{23}H_{22}Cl_3DN_2O_3S_2$ (M =546.91 g/mol): triclinic, space group P-1 (no. 2), a = 9.8161(6) Å, b = 15.6907(9) Å, c = 17.1093(10) Å, α = 85.923(2)°, β = 75.425(2)°, γ = 81.516(2)°, V = 2520.9(3) Å^3, Z = 4, T = 120 K, μ(MoKα) = 0.558 mm^{-1}, *Dcalc* = 1.441 g/cm^3, 56721 reflections measured (4.326° ≤ 2Θ ≤ 60.262°), 14845 unique (R_{int} = 0.0561, R_{sigma} = 0.0555) which were used in all calculations. The final R_1 was 0.0504 (I > 2σ(I)) and wR_2 was 0.1321 (all data)

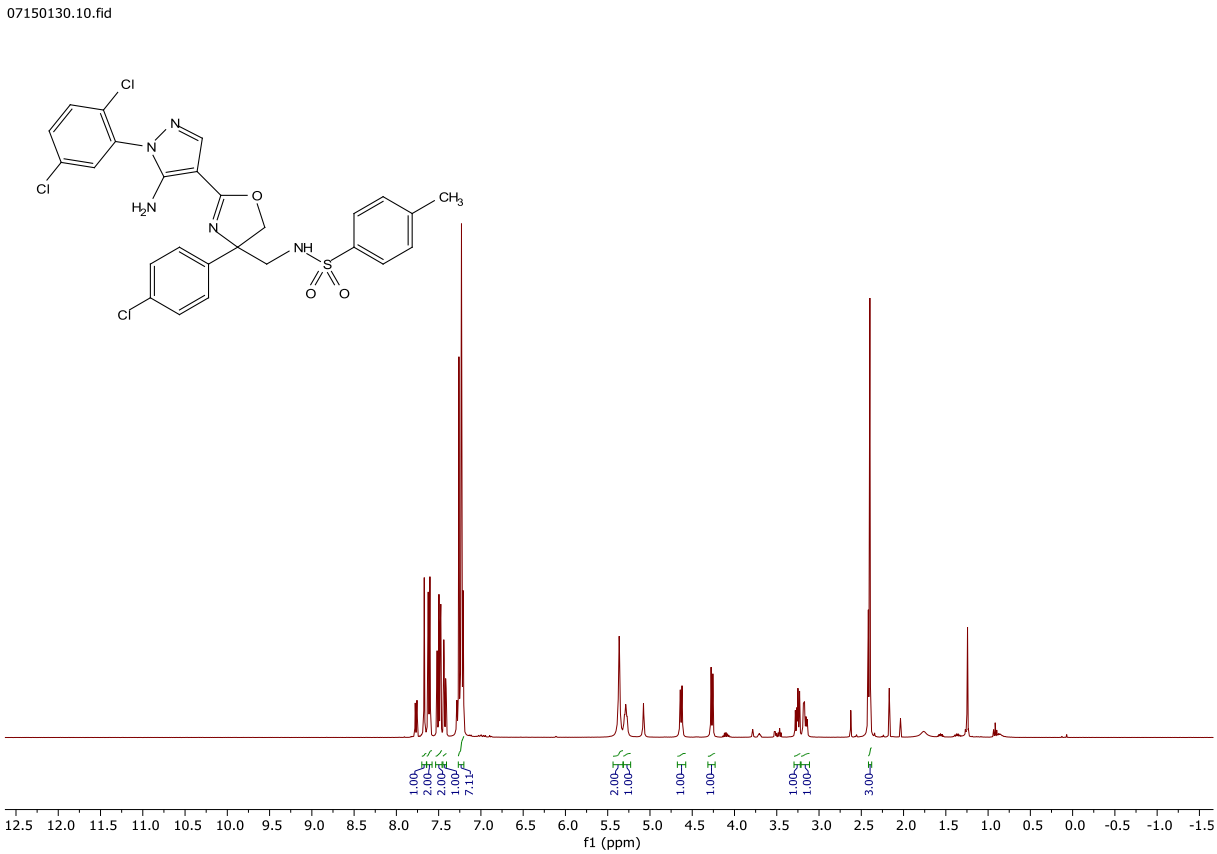
Compound 2-177 ^{1}H NMR (400 MHz, $CDCl_3$)



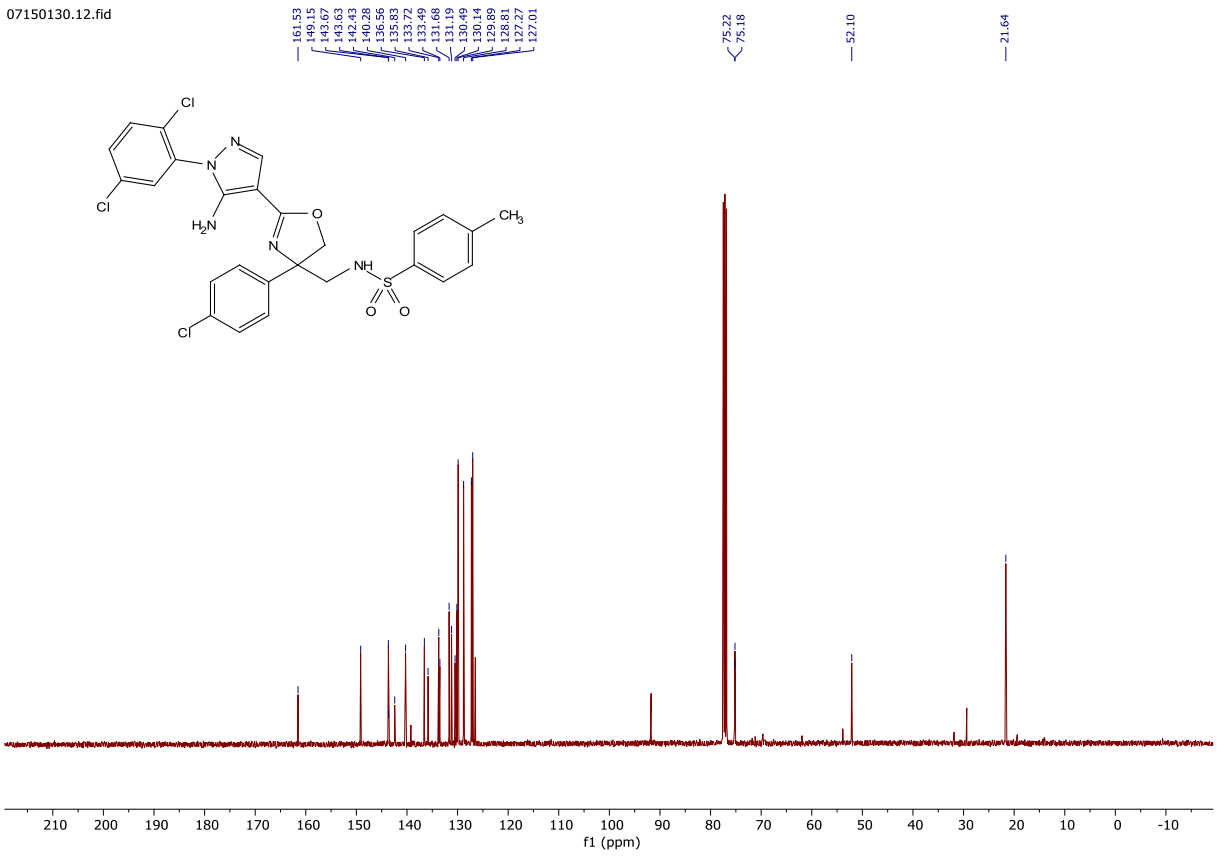
Compound **2-177** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



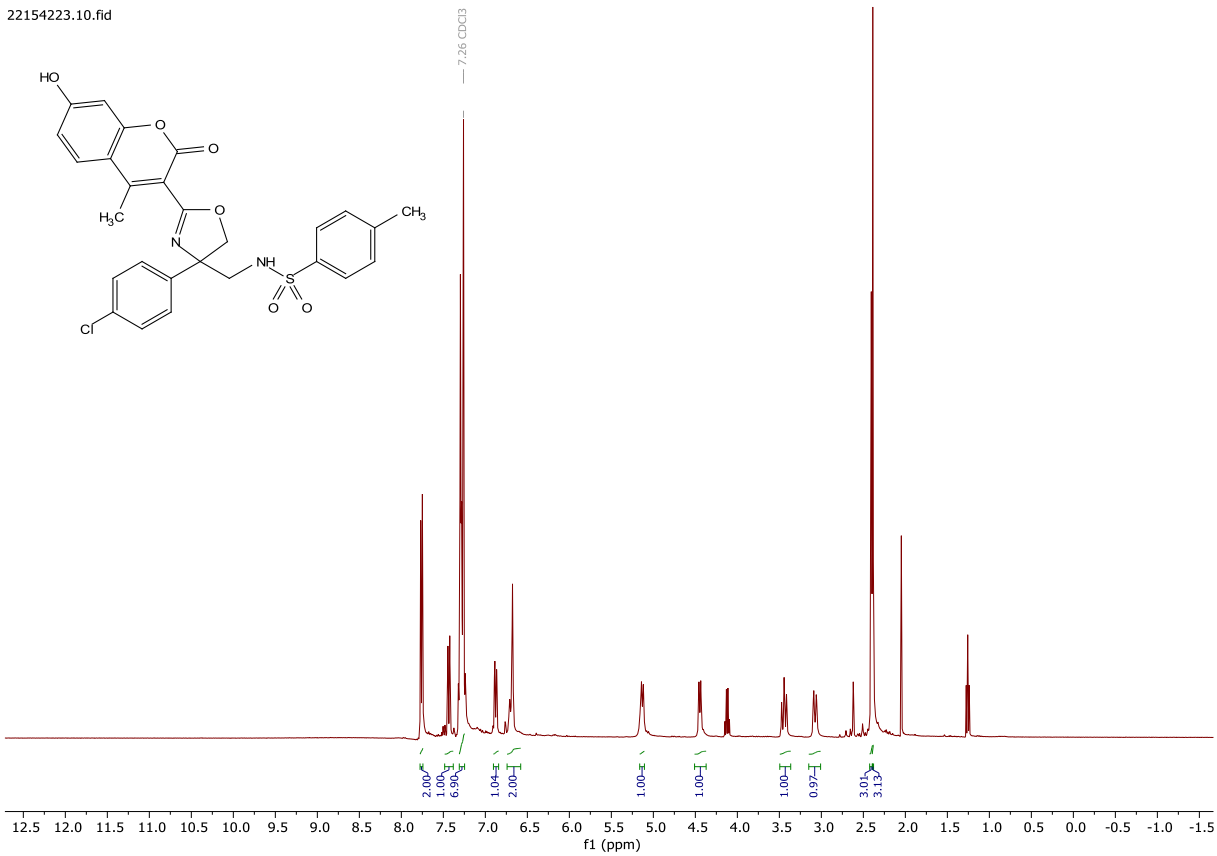
Compound 2-175 ^{1}H NMR (400 MHz, $CDCl_3$)



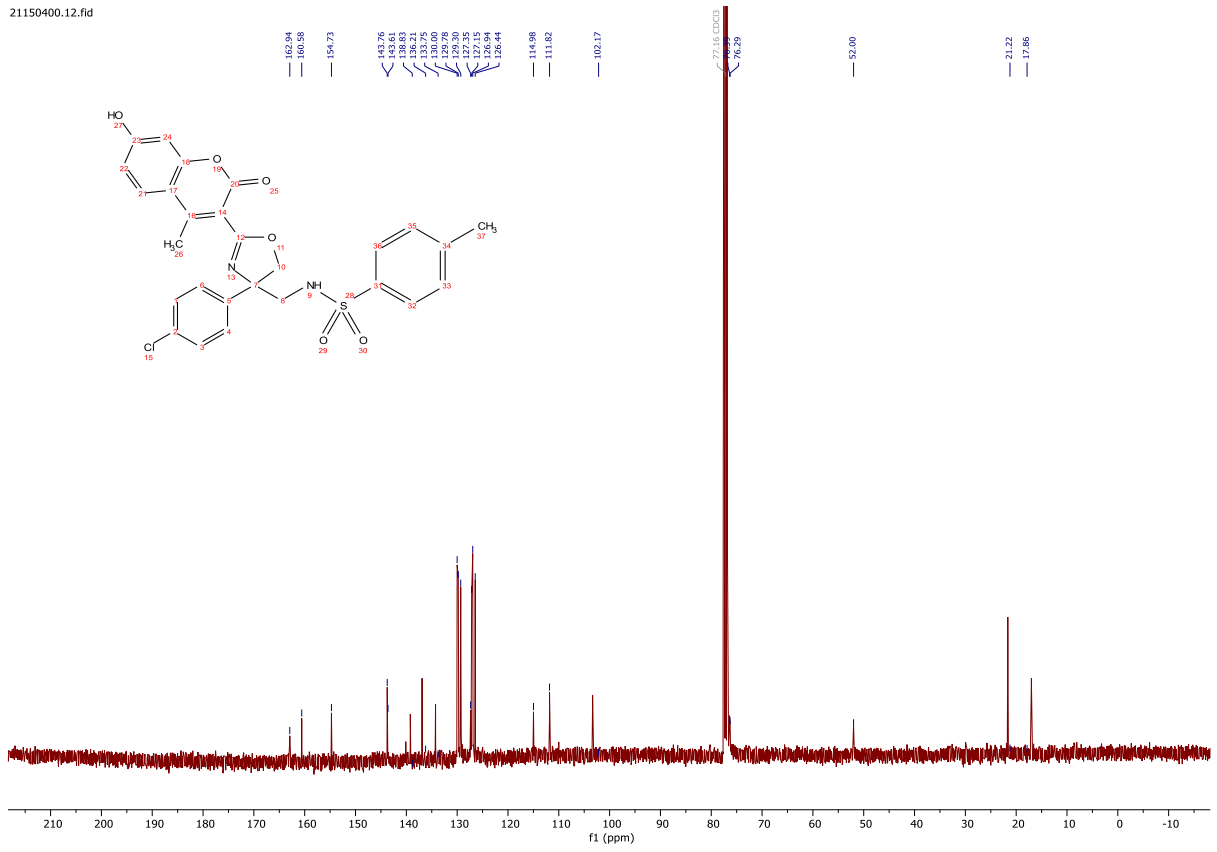
Compound **2-178** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



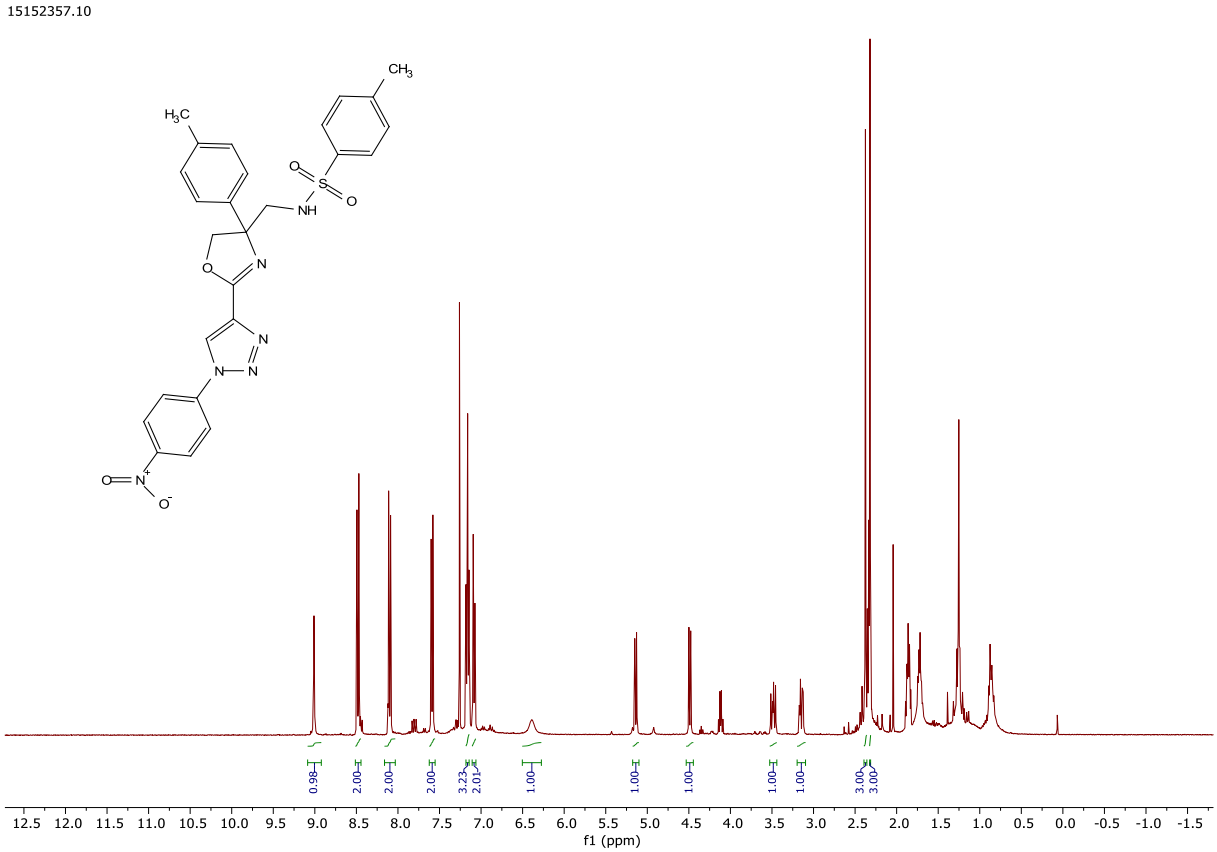
Compound 2-179 ^{1}H NMR (400 MHz, $CDCl_3$)



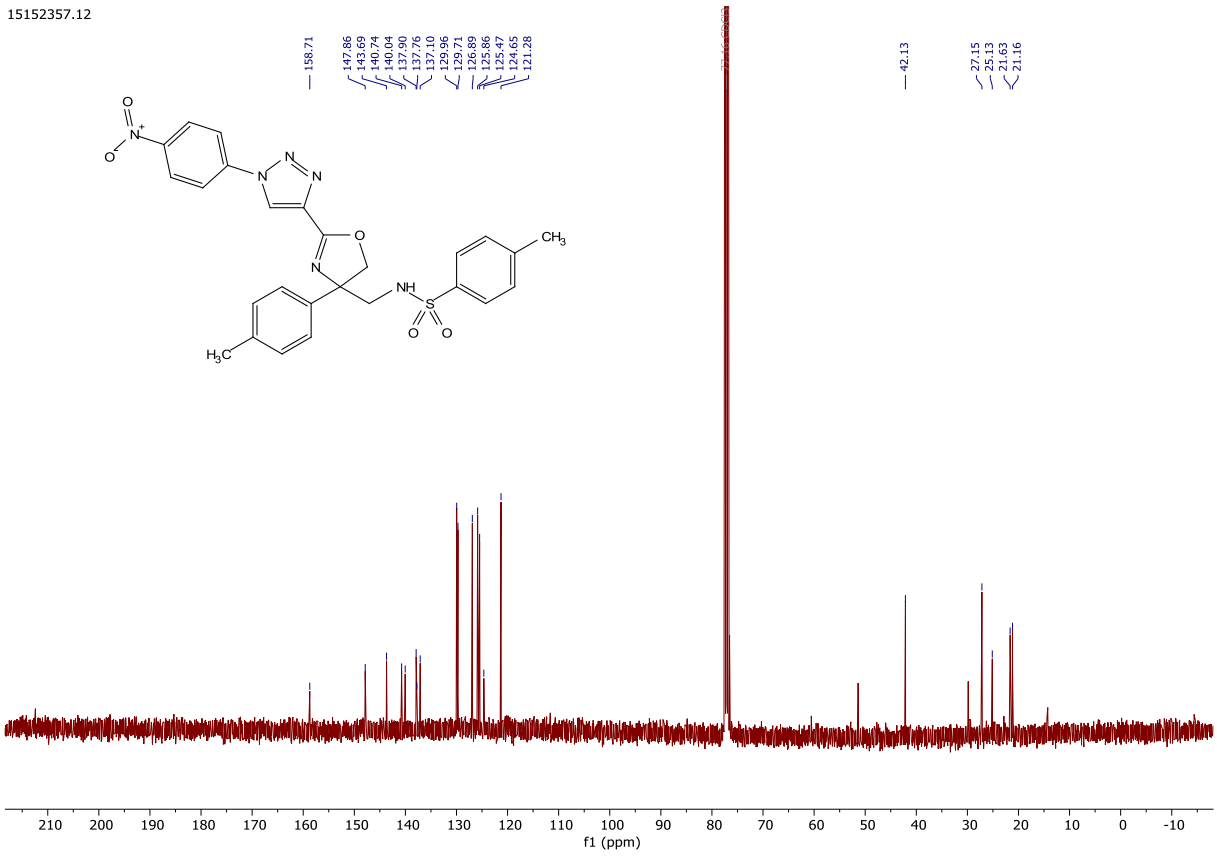
Compound **2-179** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



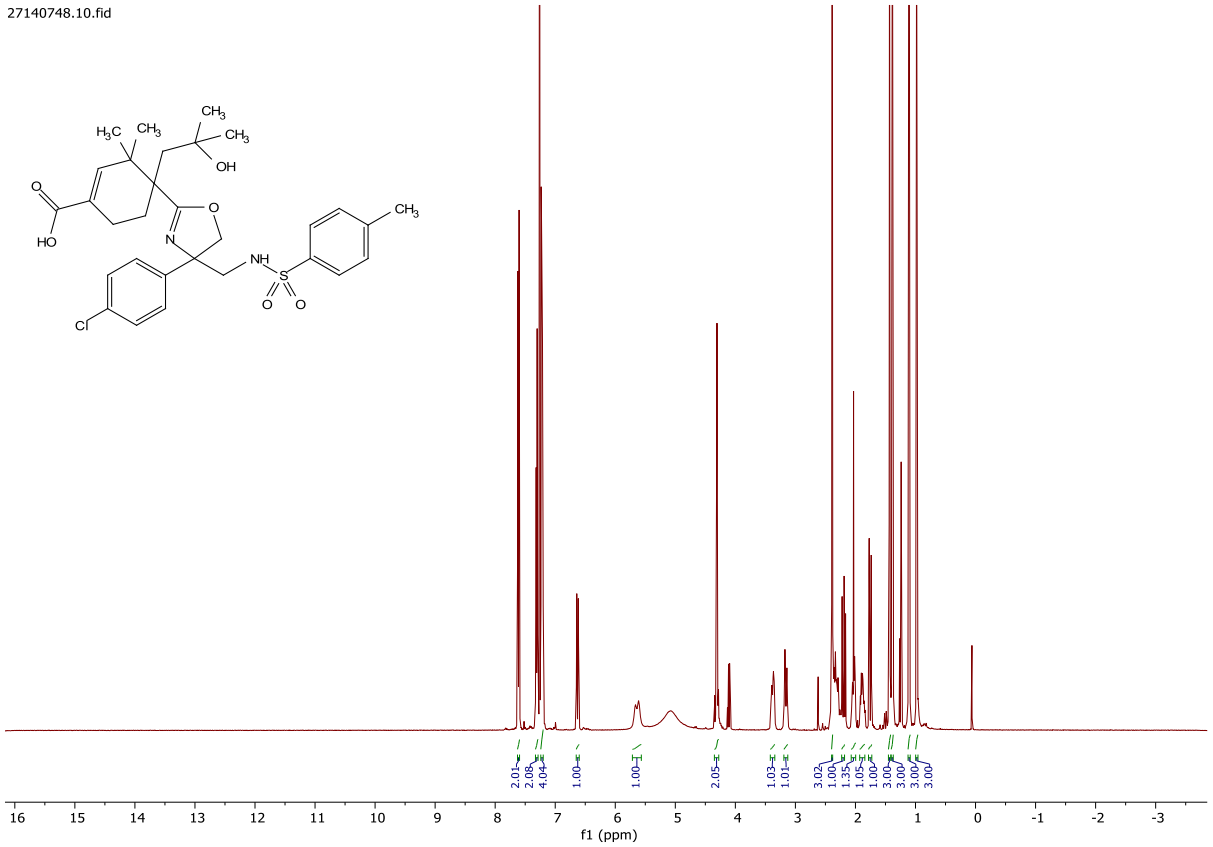
Compound 2-180 ^{1}H NMR (400 MHz, $CDCl_3$)



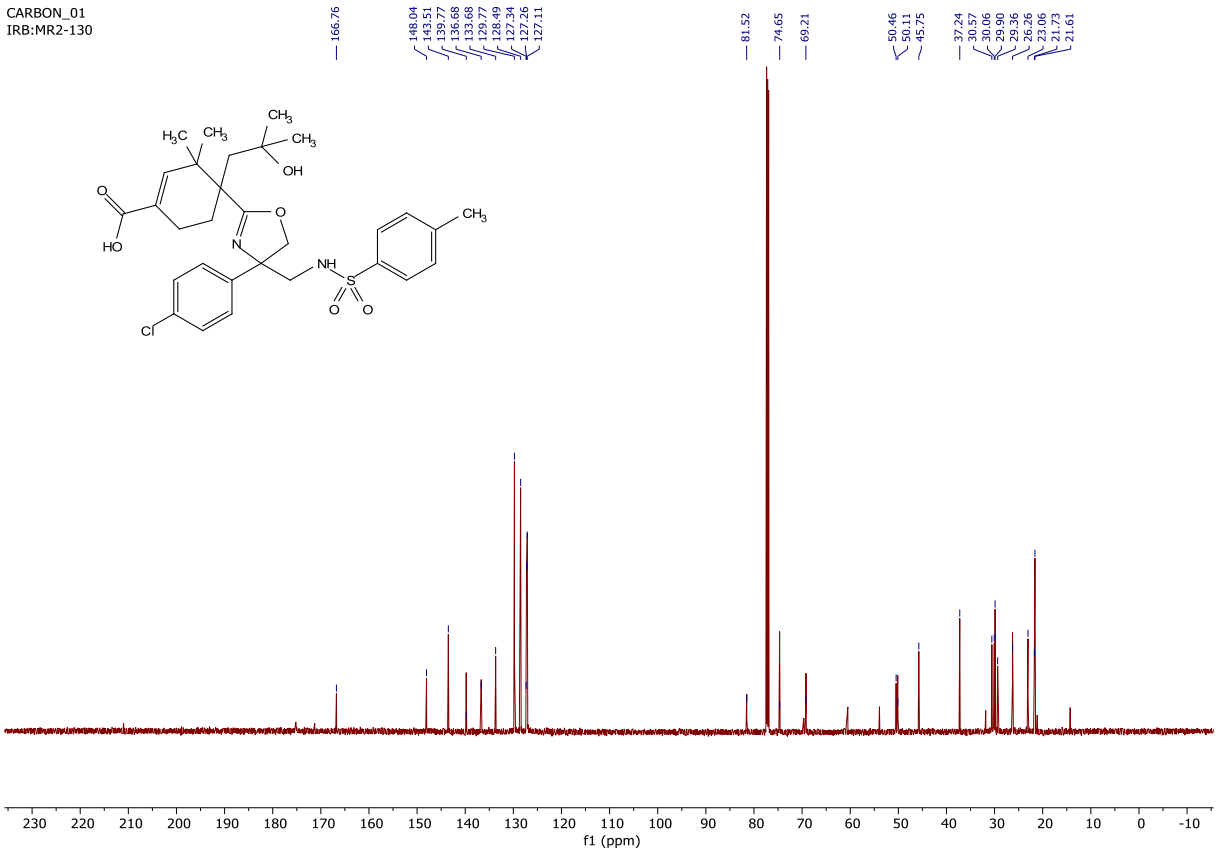
Compound **2-180** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



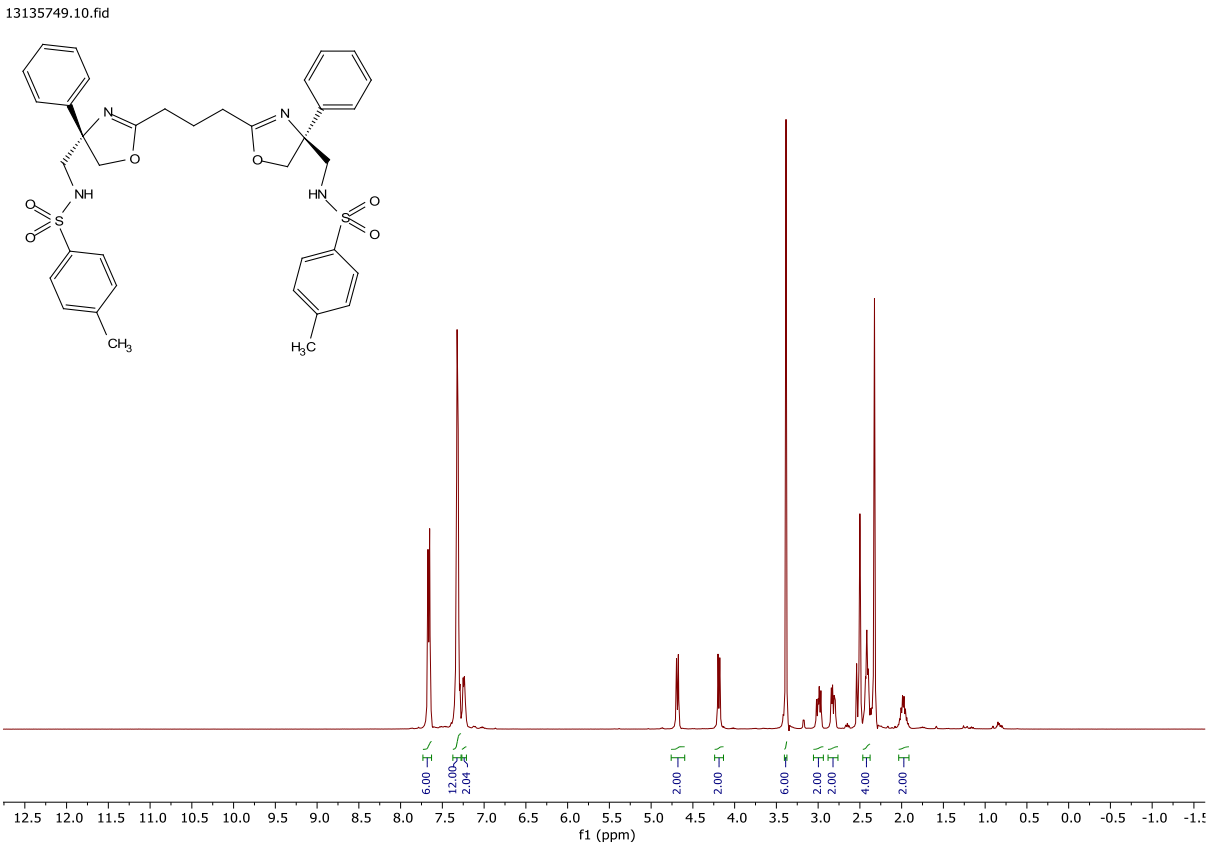
Compound 2-181 ^{1}H NMR (400 MHz, $CDCl_3$)



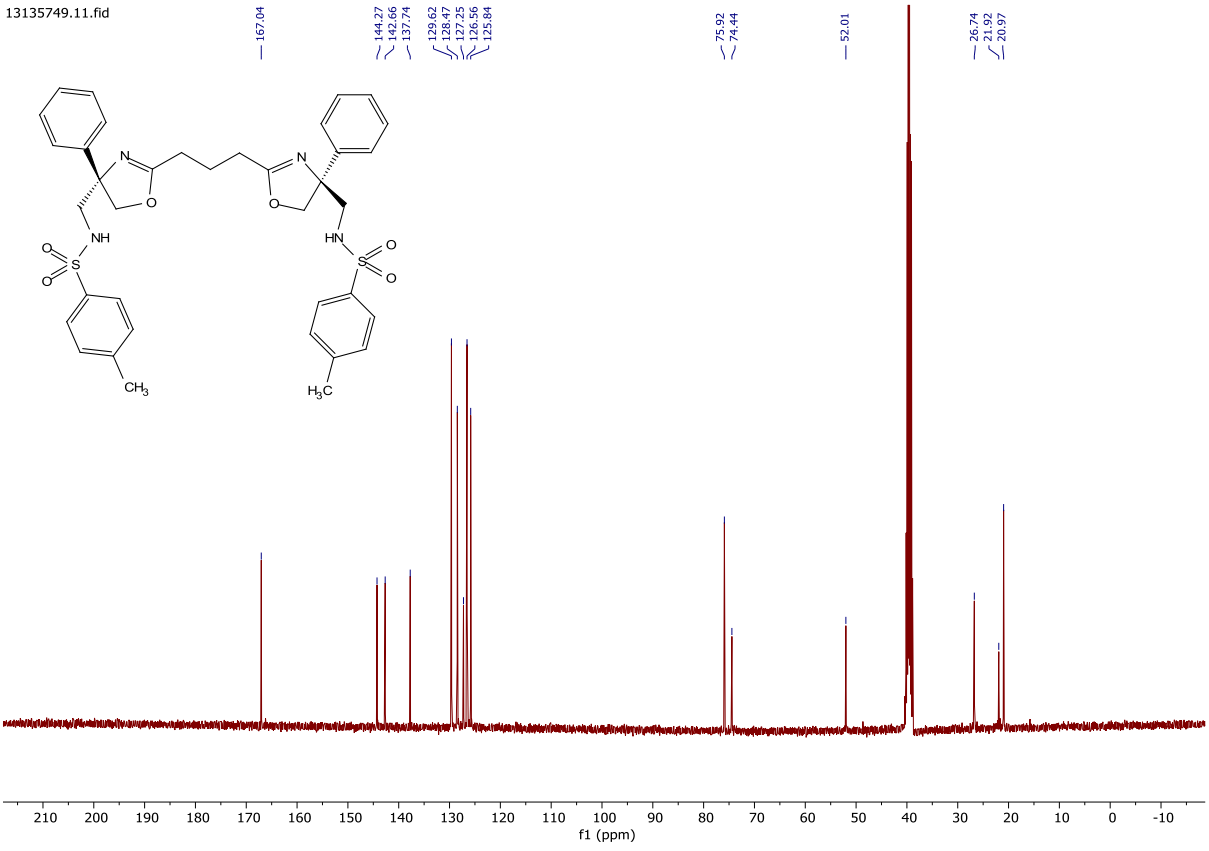
Compound **2-181** $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



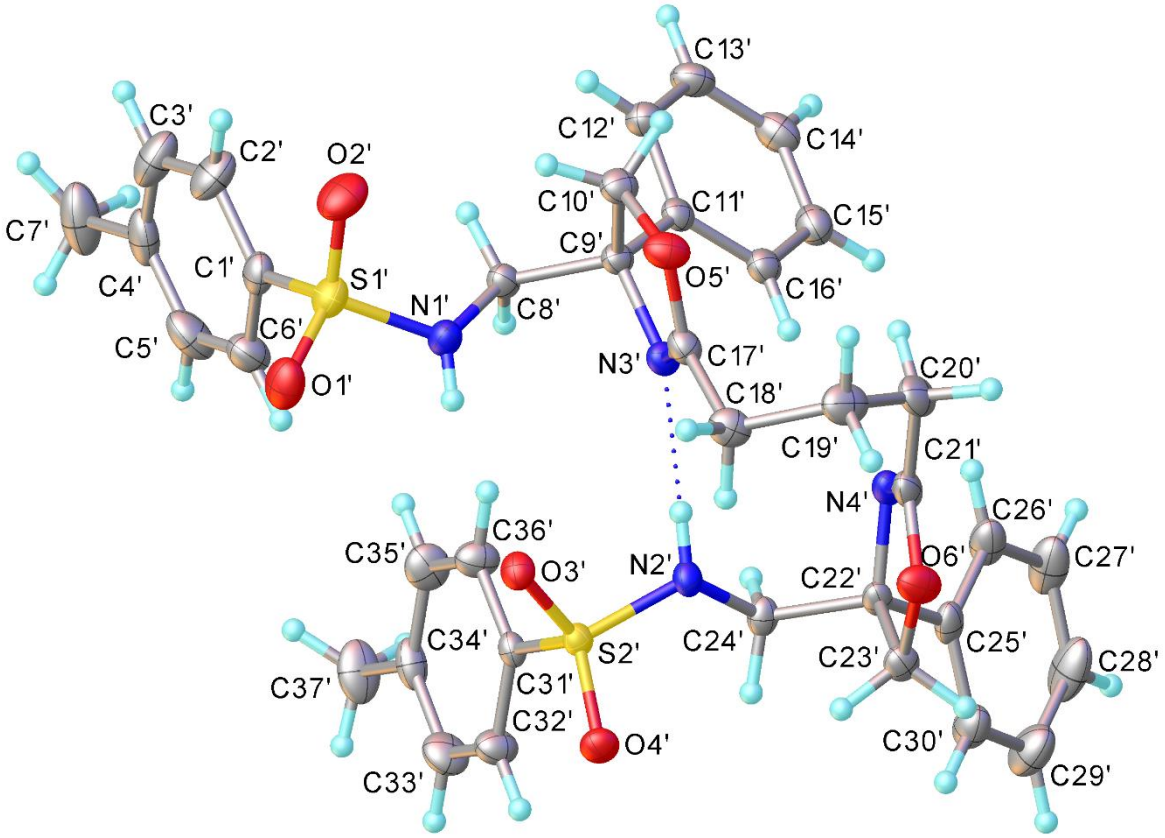
Compound 2-193 ^{1}H NMR (400 MHz, DMSO)



Compound **2-193** ^{13}C{^{1}H} NMR (101 MHz, DMSO)



Compound 2-193 X-ray structure



Atomic displacement ellipsoids are drawn at the 50% probability level.

Compound 4-20 was crystallised by solvent evaporation using a mixture Hexane: EtOAc

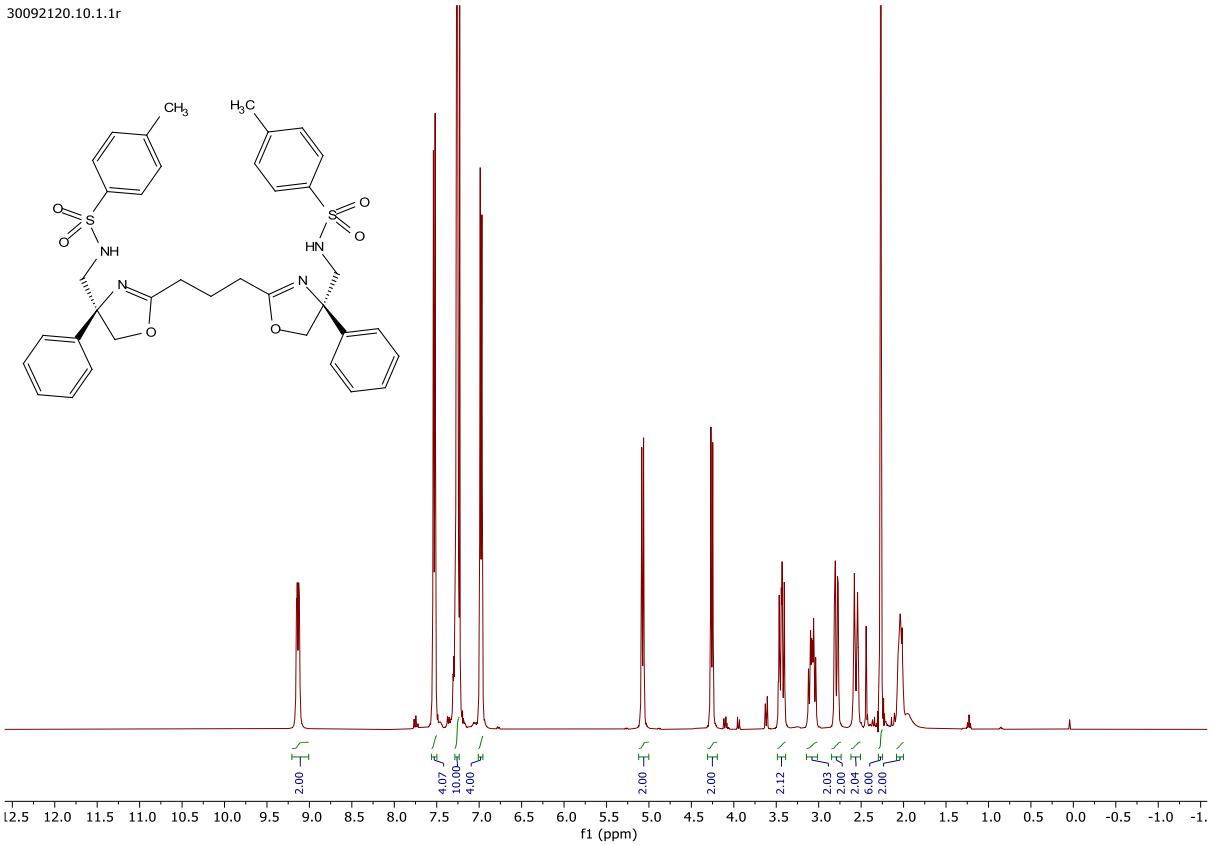
Experimental

Single crystals of $C_{37}H_{41}N_4O_6S_2$ were A suitable crystal was selected on a D8V_Mo diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

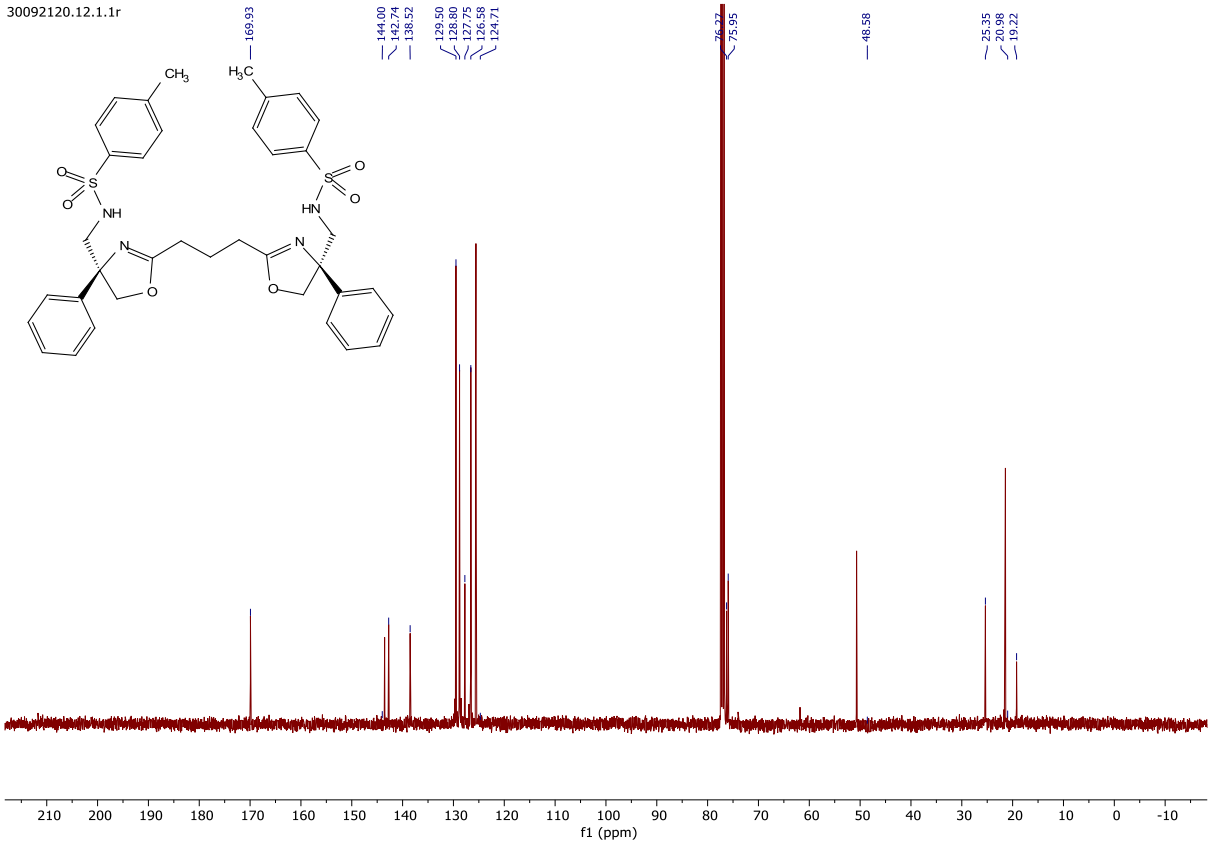
7) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
8) Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
9) Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data for $C_{37}H_{40}N_4O_6S_2$ (M =710.98 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 11.8945(9) Å, b = 21.4091(15) Å, c = 28.158(2) Å, β = 96.410(3)°, V = 7125.5(9) Å^3, Z = 8, T = 120 K, μ(MoKα) = 0.202 mm^{-1}, $Dcalc$ = 1.325 g/cm^3, 139564 reflections measured (3.888° ≤ 2Θ ≤ 58°), 19071 unique (R_{int} = 0.0453, R_{sigma} = 0.0323) which were used in all calculations. The final R_1 was 0.0522 (I > 2σ(I)) and wR_2 was 0.1309 (all data)

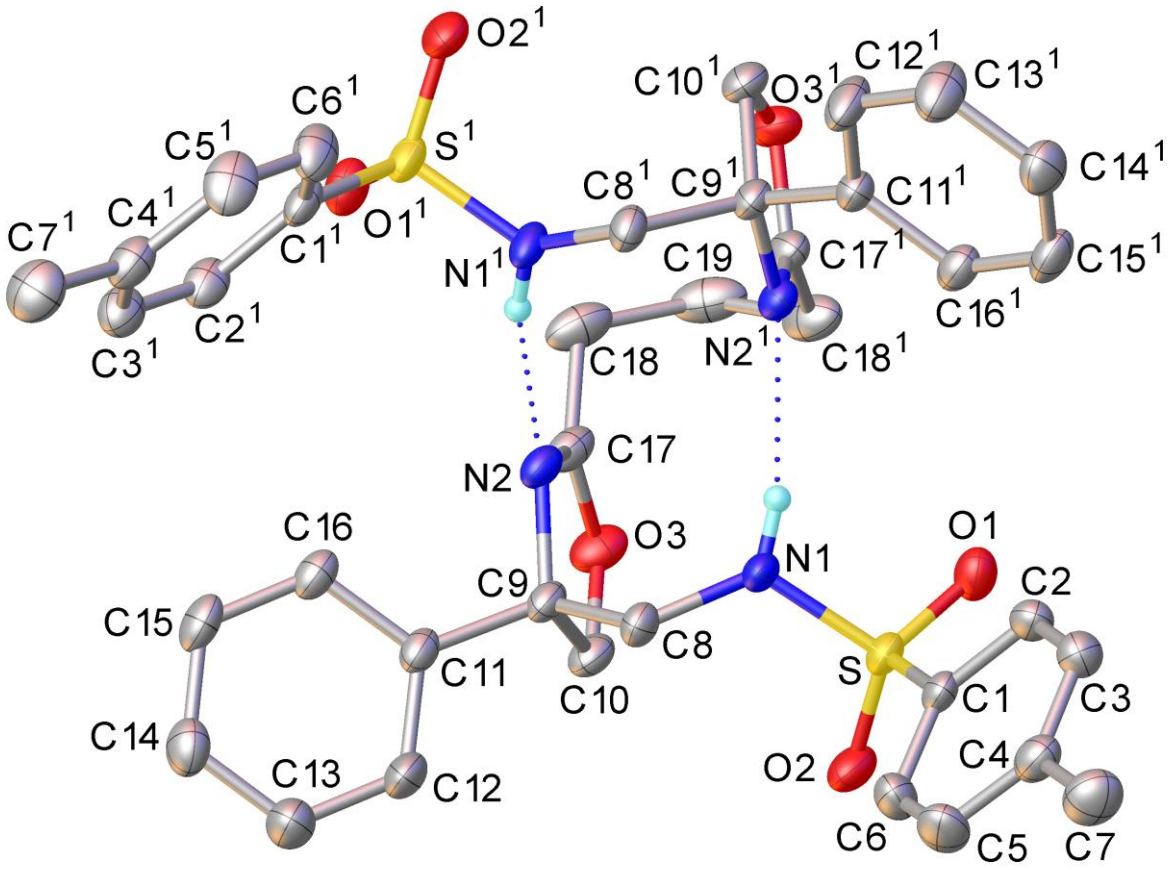
Compound 2-194 ^{1}H NMR (400 MHz, $CDCl_3$)



Compound **2-194** $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



Compound 2-194 X-ray structure



Atomic displacement ellipsoids are drawn at the 50% probability level.

Compound 4-21 was crystallised by solvent evaporation using a mixture Hexane: EtOAc

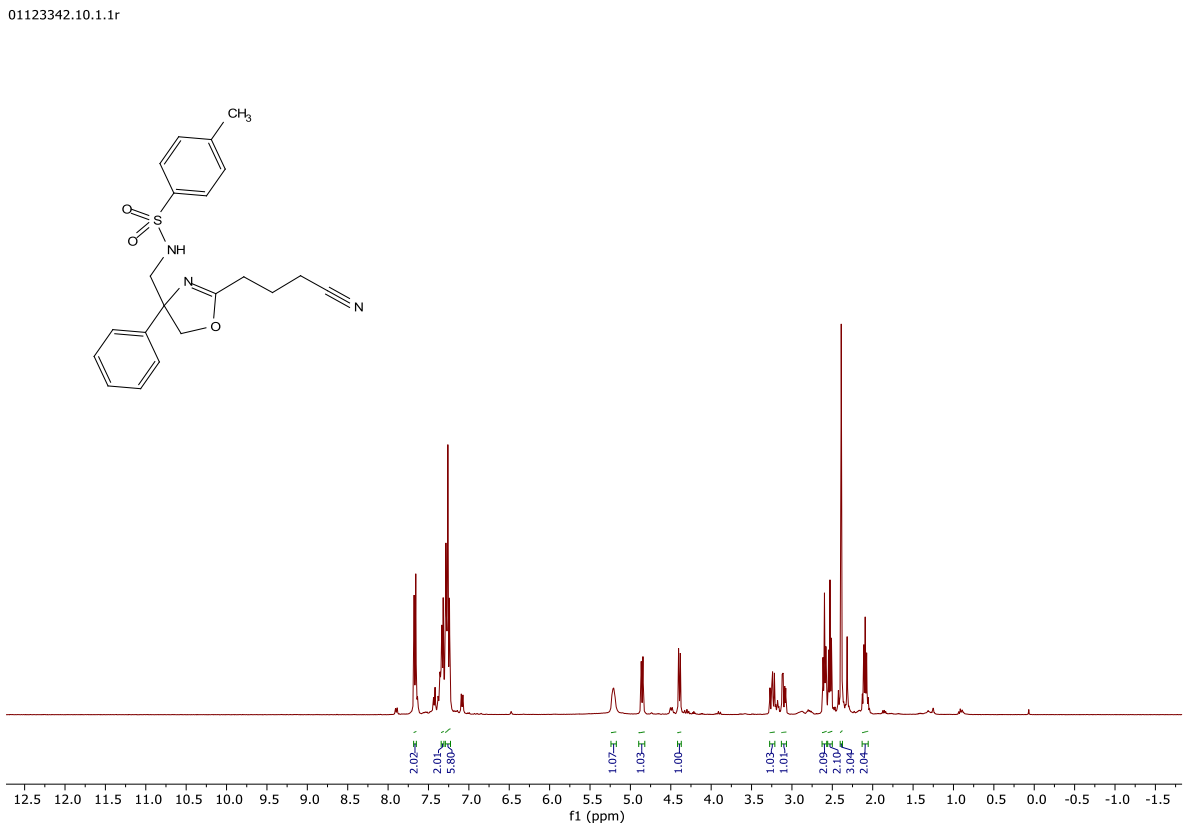
Experimental

Single crystals of $C_{37}H_{40}N_4O_6S_2$ were A suitable crystal was selected on a D8V_Mo diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

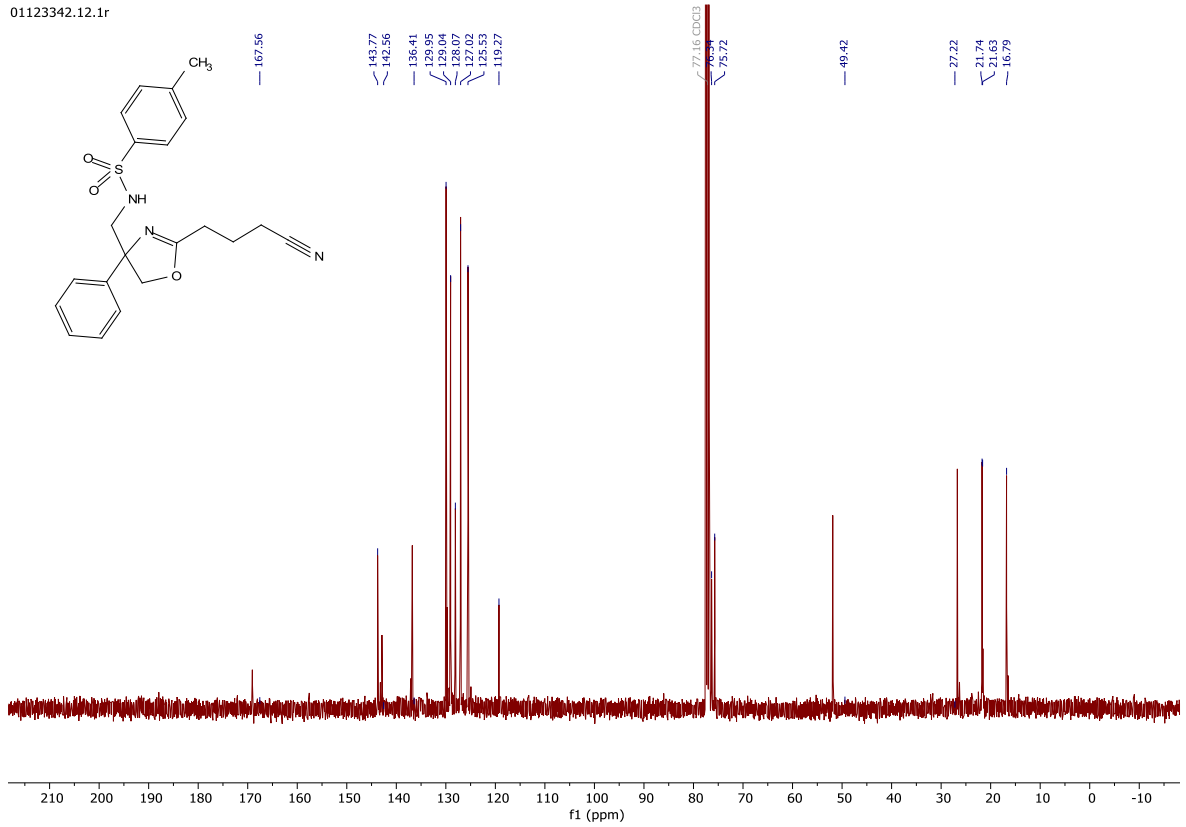
1) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2) Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
3) Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data for $C_{37}H_{40}N_4O_6S_2$ (M =700.85 g/mol): monoclinic, space group C2/c (no. 15), a = 15.0965(9) Å, b = 12.1682(7) Å, c = 21.8118(12) Å, β = 94.212(2)°, V = 3995.9(4) Å^3, Z = 4, T = 120 K, μ(MoKα) = 0.179 mm^{-1}, $Dcalc$ = 1.165 g/cm^3, 36802 reflections measured (4.304° ≤ 2Θ ≤ 54.962°), 4596 unique (R_{int} = 0.0435, R_{sigma} = 0.0288) which were used in all calculations. The final R_1 was 0.0385 (I > 2σ(I)) and wR_2 was 0.1092 (all data).

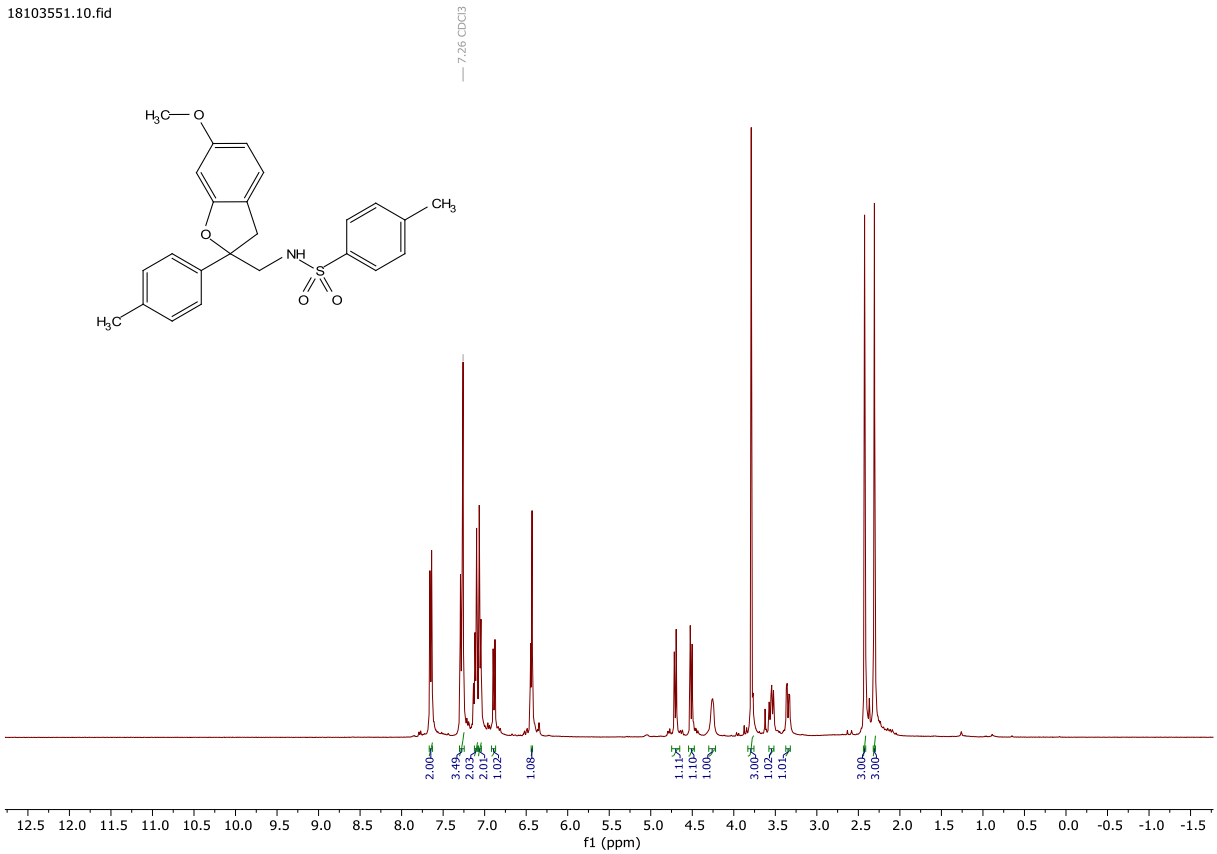
Compound 2-195 ^{1}H NMR (400 MHz, $CDCl_3$)



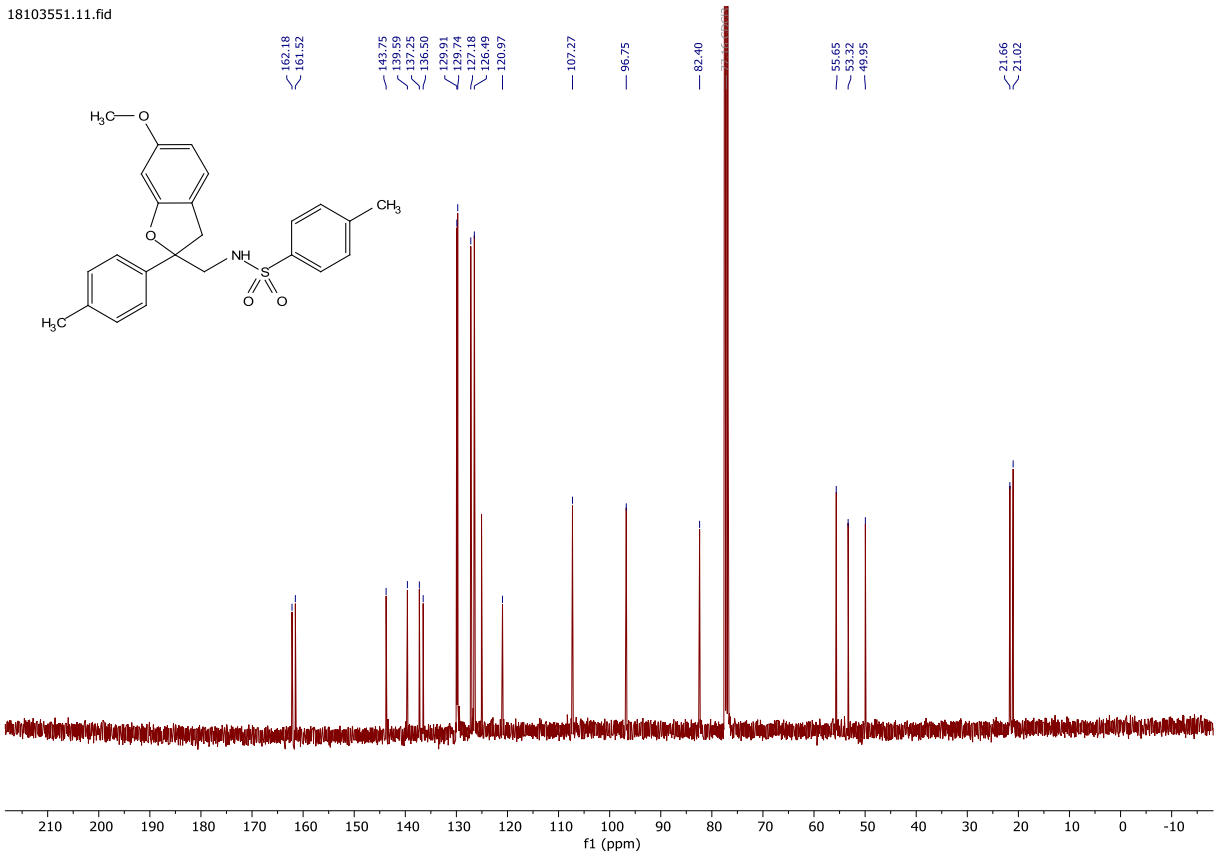
Compound **2-195** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



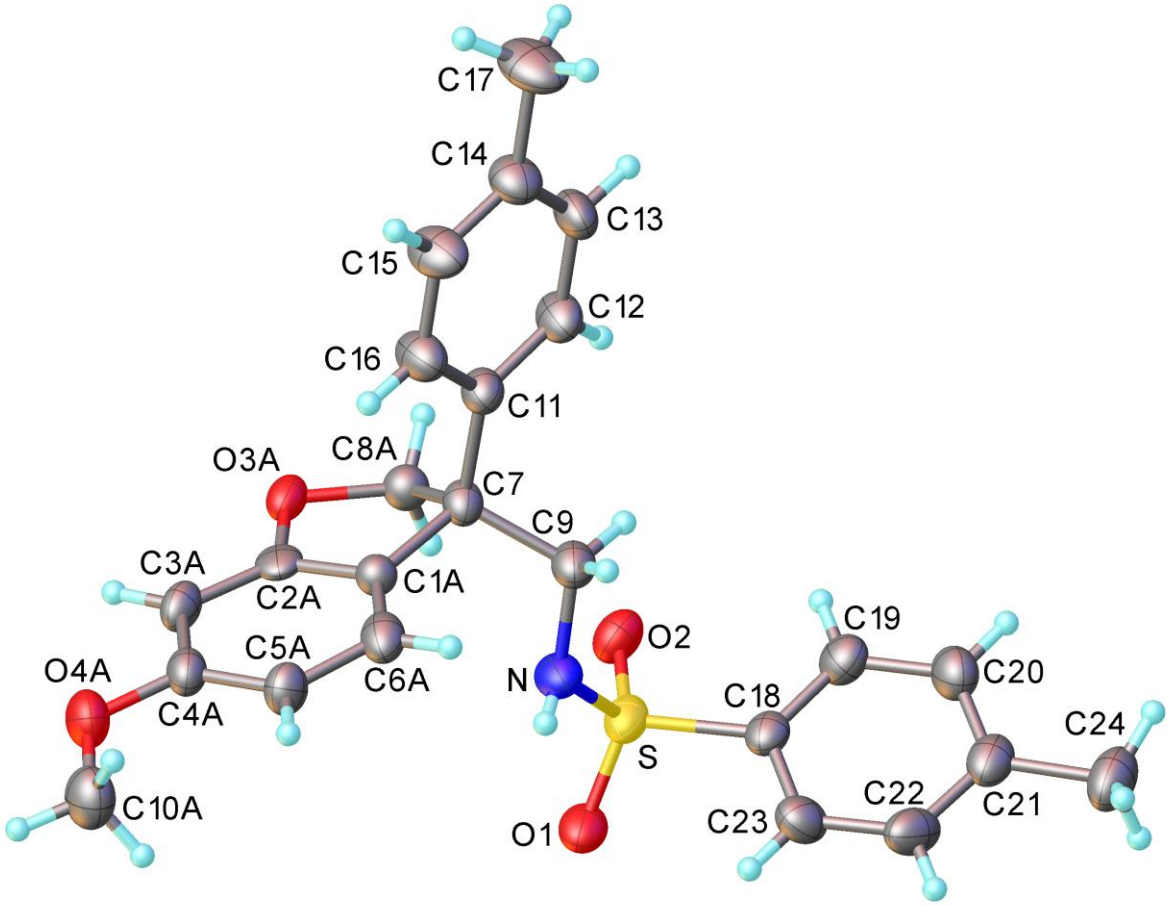
Compound 2-197 ^{1}H NMR (400 MHz, $CDCl_3$)



Compound **2-197** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



Compound 2-197 X-ray structure



Atomic displacement ellipsoids are drawn at the 50% probability level.

Compound 4-7 was crystallised by solvent evaporation using a mixture Hexane: EtOAc

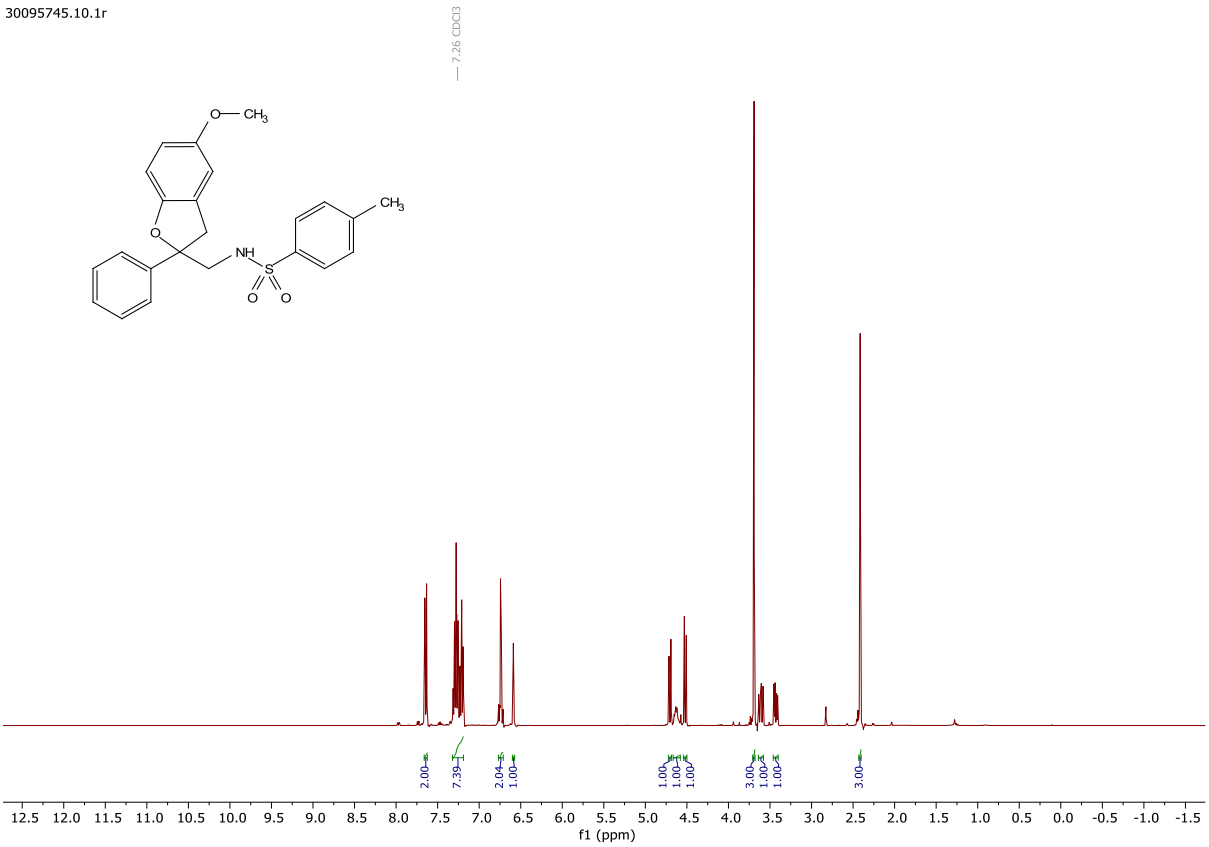
Experimental

Single crystals of $C_{24}H_{25}NO_4S$ were A suitable crystal was selected on a D8V_Mo diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

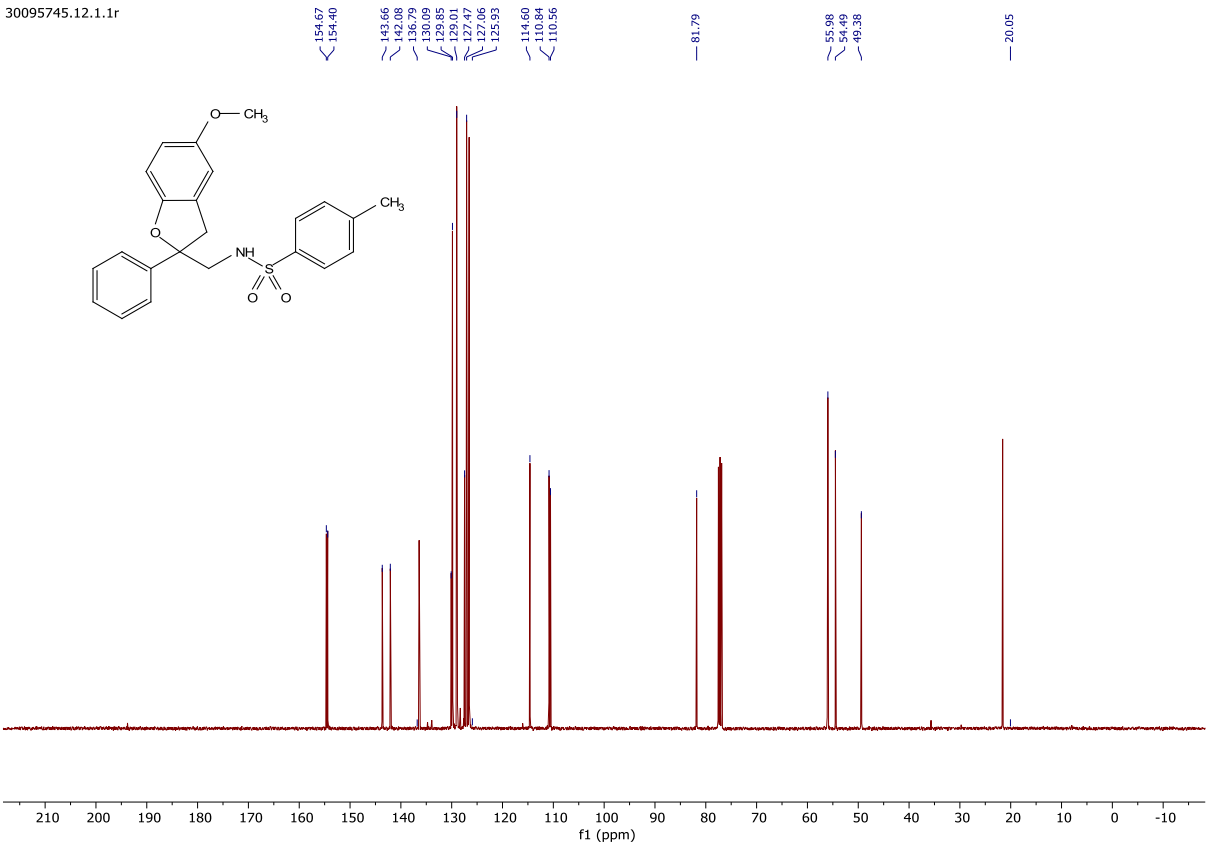
4) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
5) Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
6) Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data Crystal Data for $C_{24}H_{25}NO_4S$ (*M* =423.51 g/mol): monoclinic, space group $P2_1/n$ (no. 14), *a* = 10.9761(8) Å, *b* = 11.2566(8) Å, *c* = 17.2670(13) Å, *β* = 98.209(2)°, *V* = 2111.5(3) Å^3, *Z* = 4, *T* = 120 K, μ(MoKα) = 0.184 mm^{-1}, *Dcalc* = 1.332 g/cm^3, 32741 reflections measured (4.146° ≤ 2Θ ≤ 50.17°), 3761 unique (R_{int} = 0.0775, R_{sigma} = 0.0604) which were used in all calculations. The final R_1 was 0.0489 (I > 2σ(I)) and wR_2 was 0.1210 (all data).

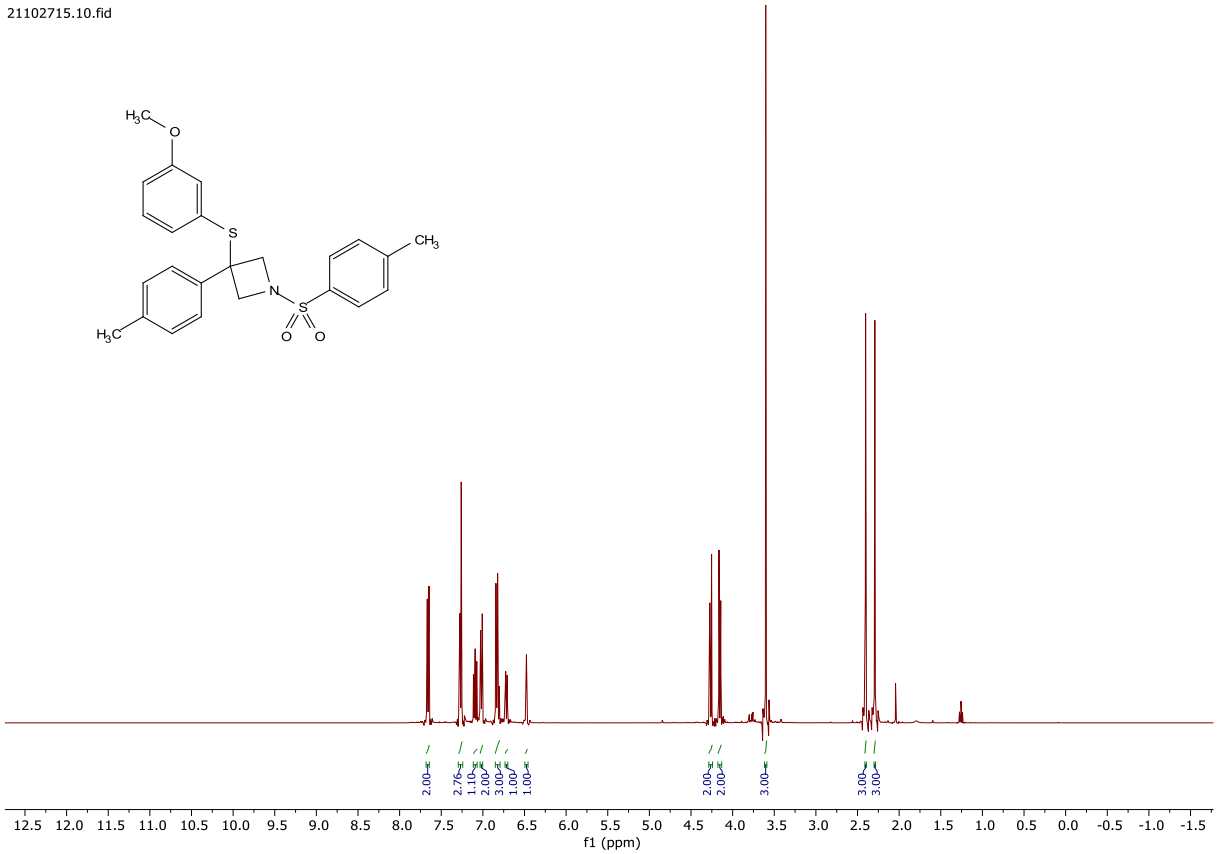
Compound 2-199 ^{1}H NMR (400 MHz, $CDCl_3$)



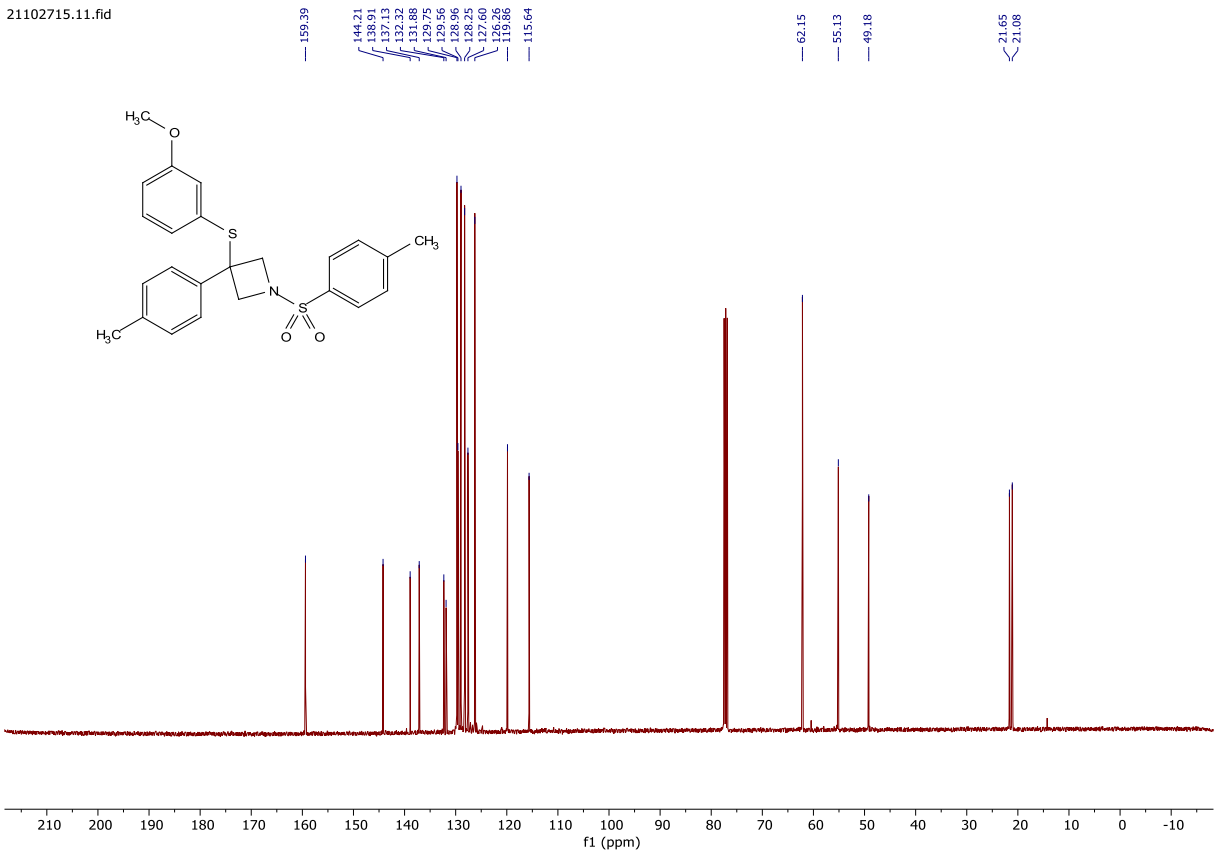
Compound **2-199** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



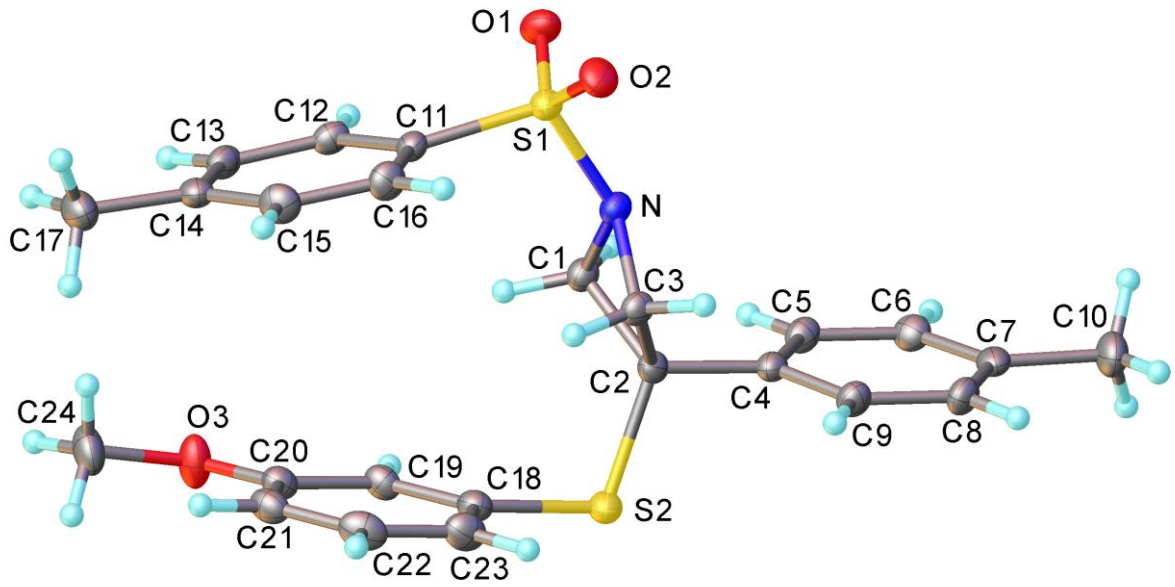
Compound 2-201 ^{1}H NMR (400 MHz, $CDCl_3$)



Compound **2-201** $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



Compound 2-202 X-ray structure



Atomic displacement ellipsoids are drawn at the 50% probability level.

Compound 9 was crystallised by solvent evaporation using a mixture Hexane: EtOAc

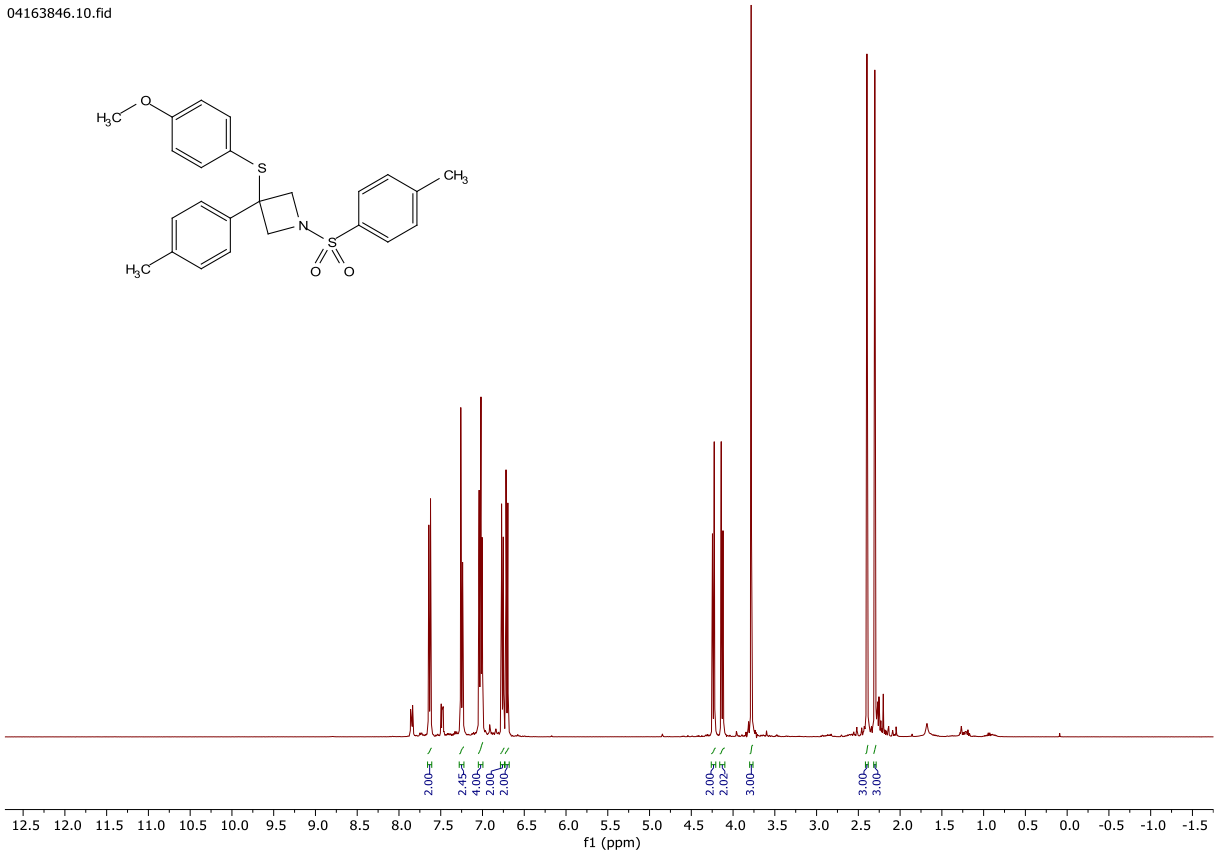
Experimental

Single crystals of $C_{24}H_{25}NO_3S_2$ were A suitable crystal was selected on a D8V_Mo diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

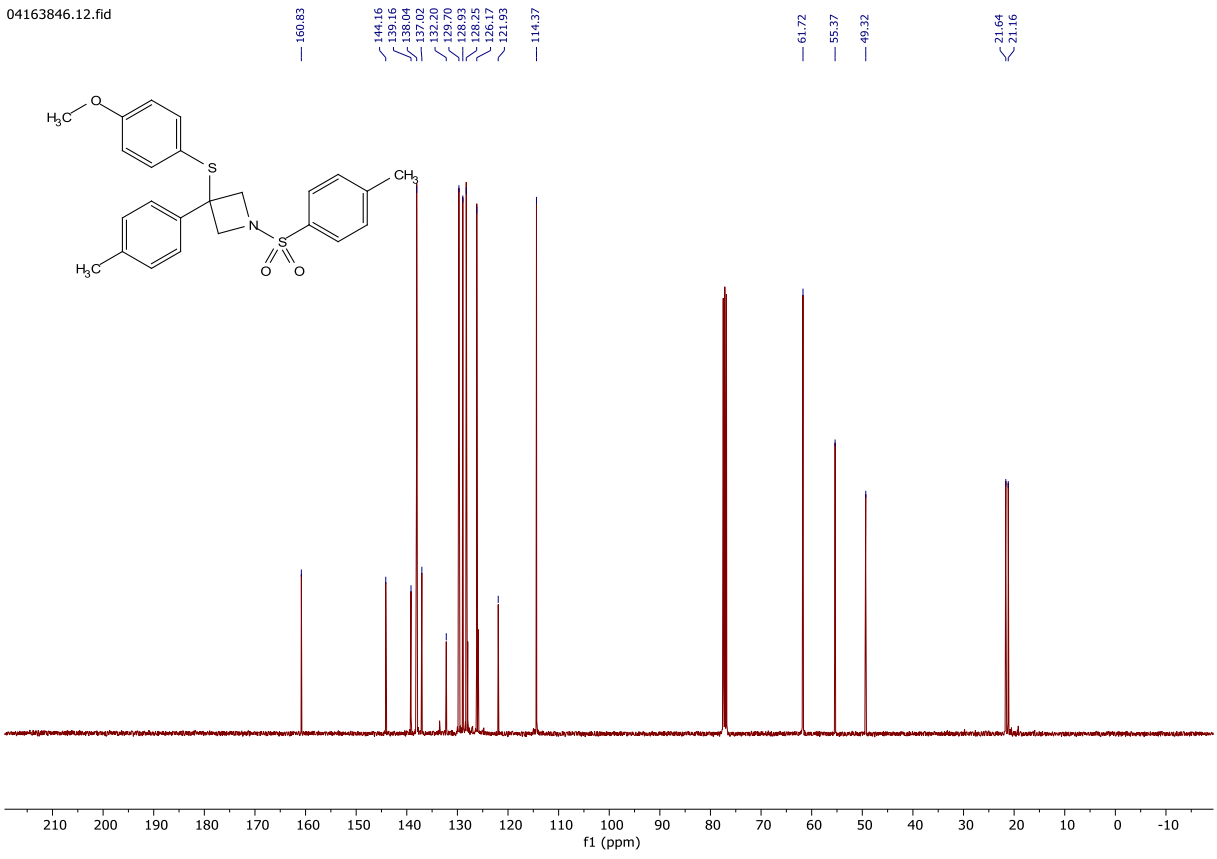
1) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2) Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
3) Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data for $C_{24}H_{25}NO_3S_2$ (M =439.57 g/mol): triclinic, space group P-1 (no. 2), a = 5.9971(2) Å, b = 19.0997(8) Å, c = 20.3305(8) Å, α = 69.0014(14)°, β = 87.1419(16)°, γ = 87.6311(16)°, V = 2170.67(15) Å^3, Z = 4, T = 120 K, μ(MoKα) = 0.271 mm^{-1}, *Dcalc* = 1.345 g/cm^3, 45131 reflections measured (4.082° ≤ 2Θ ≤ 57.398°), 11184 unique (R_{int} = 0.0425, R_{sigma} = 0.0437) which were used in all calculations. The final R_1 was 0.0386 (I > 2σ(I)) and wR_2 was 0.1009 (all data).

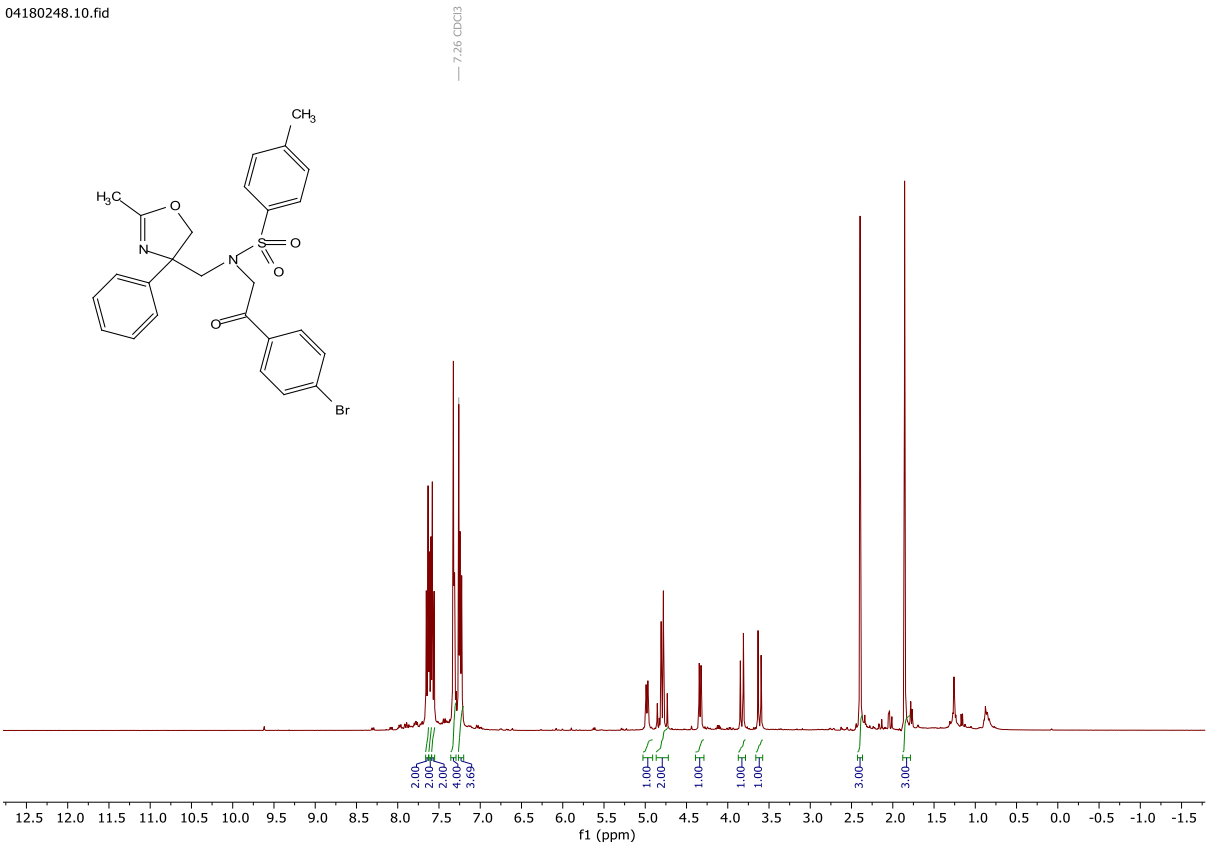
Compound 2-203 ^{1}H NMR (400 MHz, $CDCl_3$)



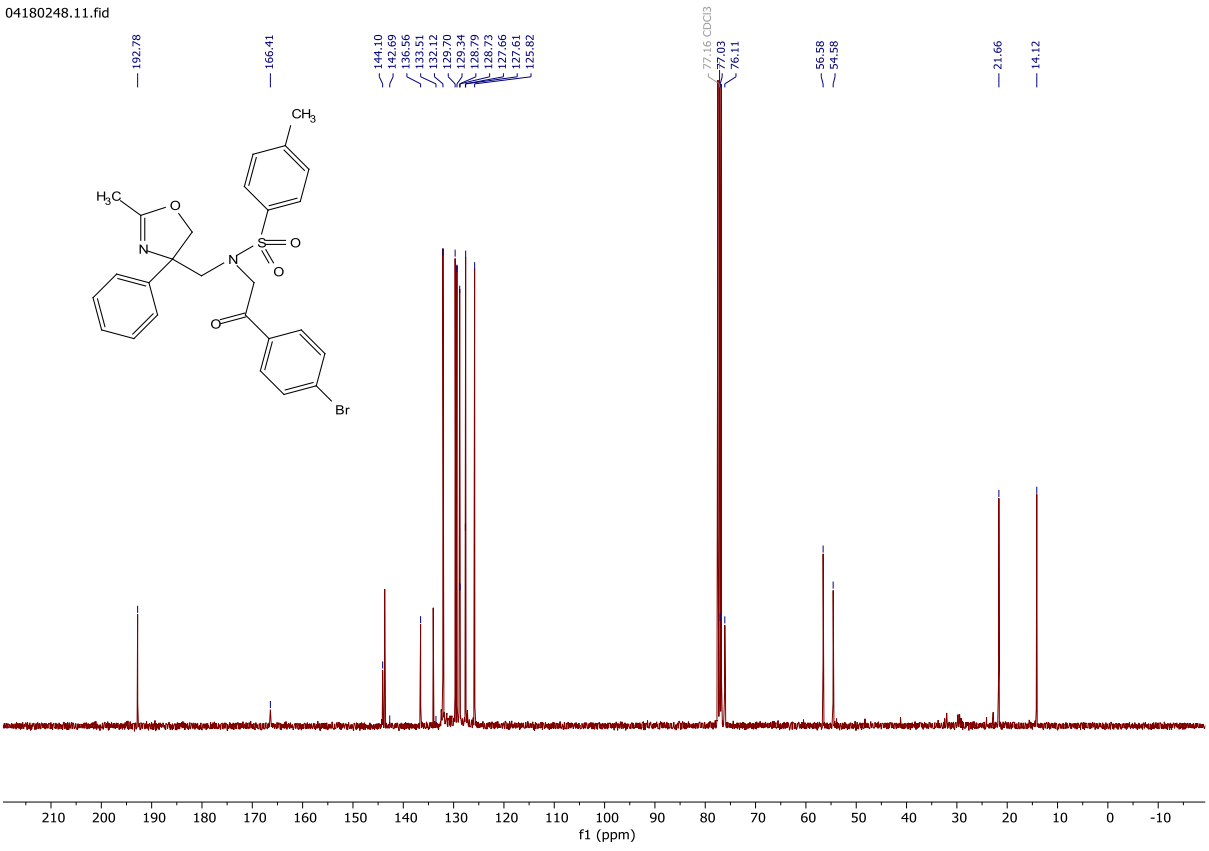
Compound **2-203** $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)



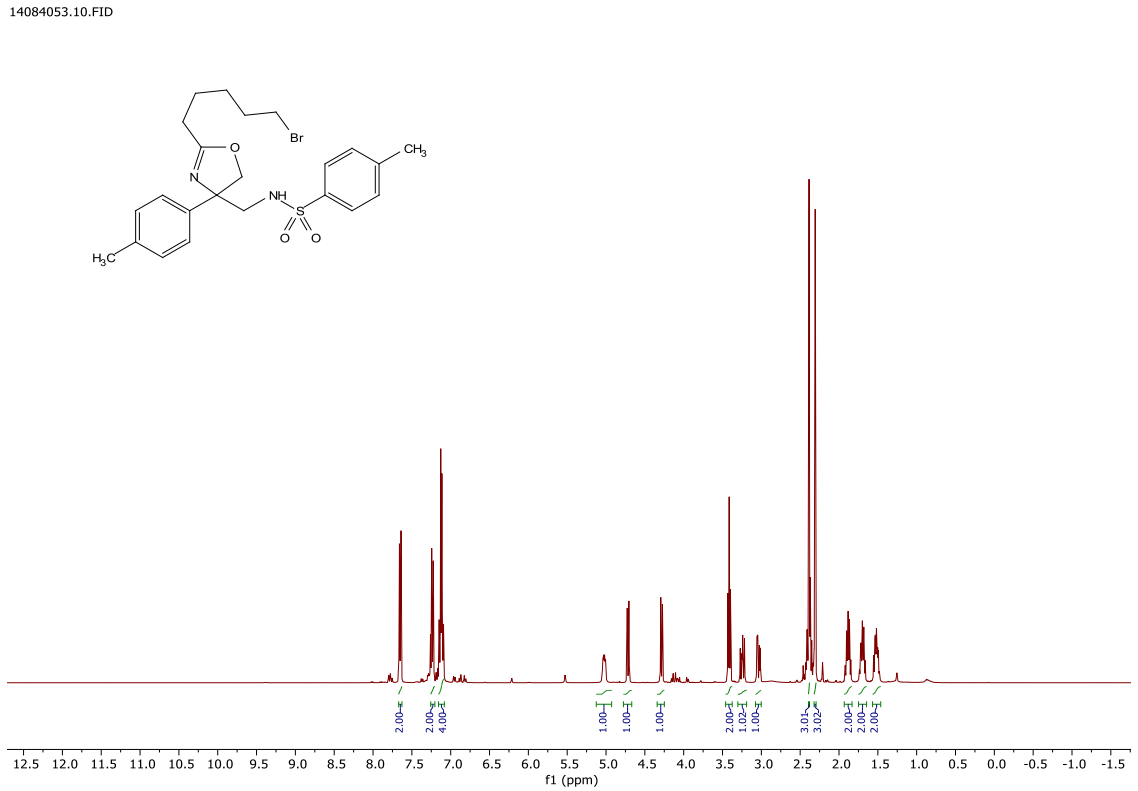
Compound 2-205 ^{1}H NMR (400 MHz, $CDCl_3$)



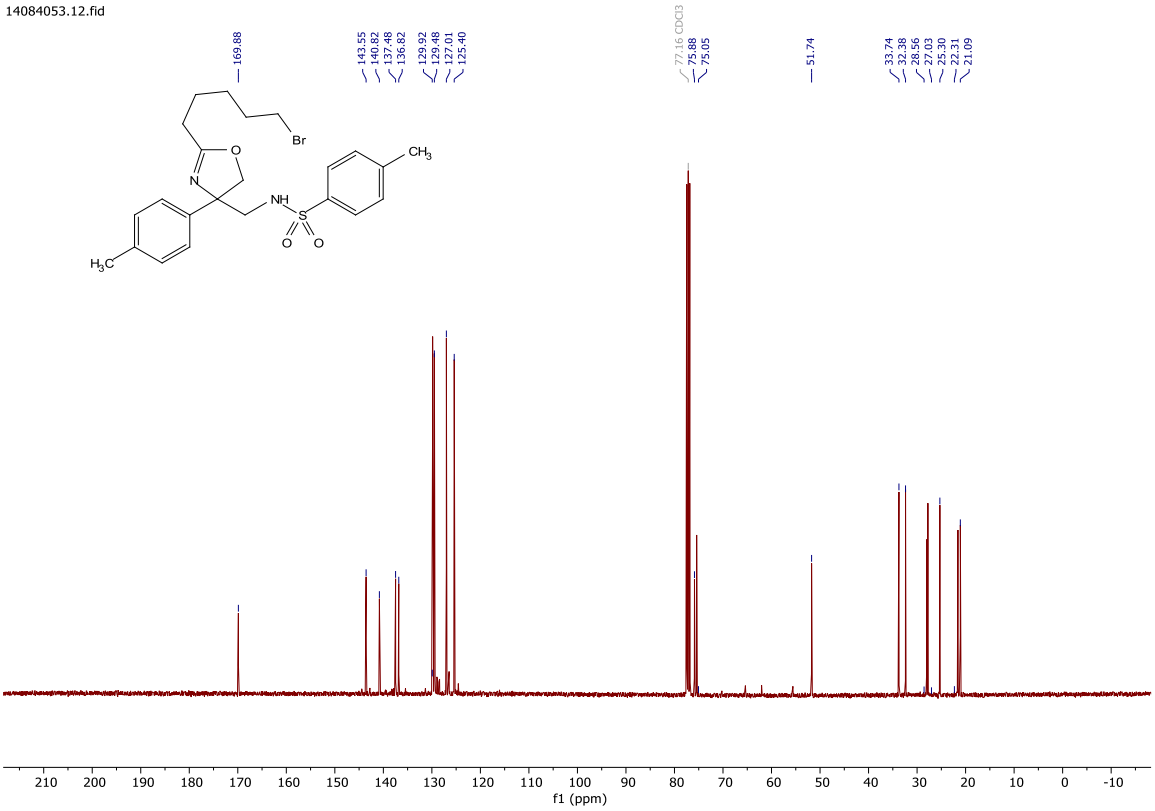
Compound **2-205** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



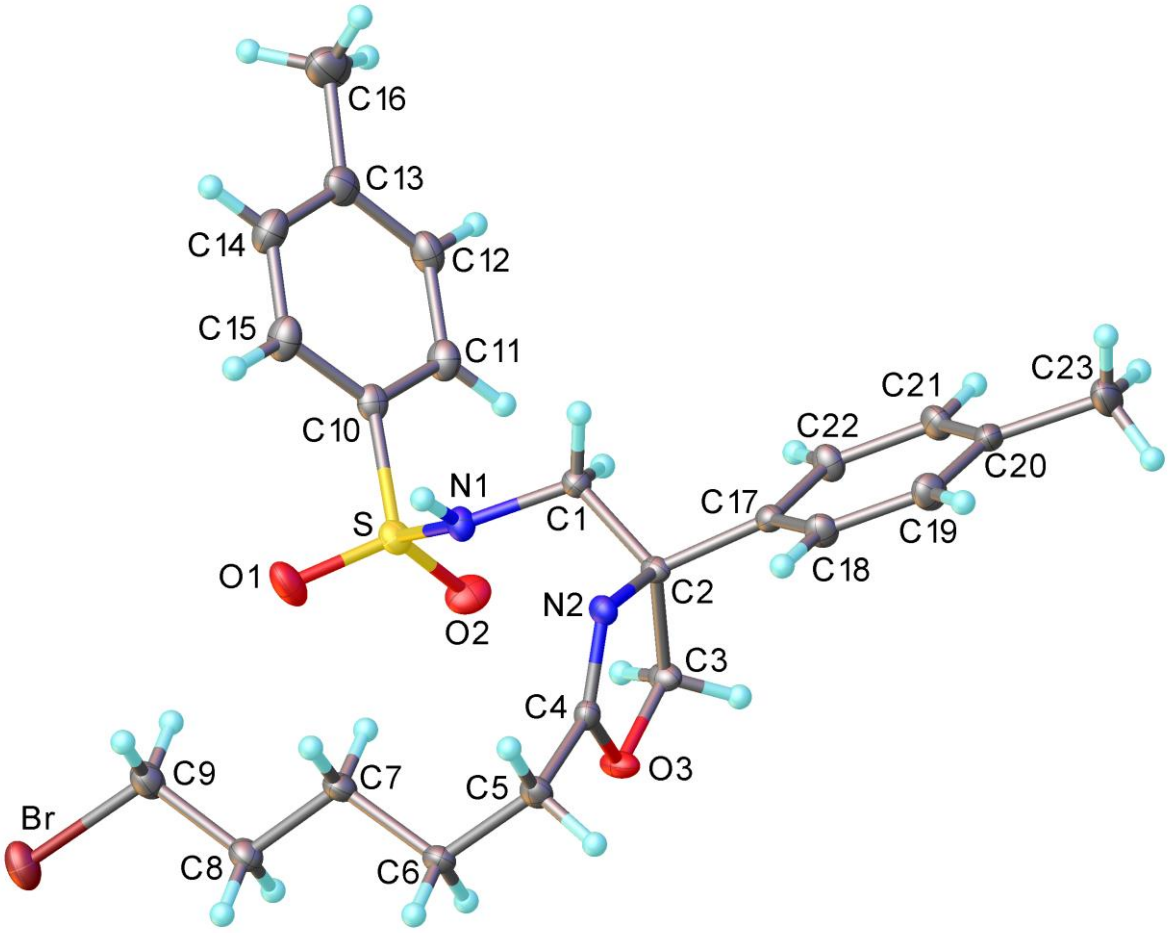
Compound 2-206 ^{1}H NMR (400 MHz, $CDCl_3$)



Compound **2-206** ^{13}C{^{1}H} NMR (101MHz, $CDCl_3$)



Compound 2-206 X-ray structure



Atomic displacement ellipsoids are drawn at the 50% probability level.

Compound 4-23 was crystallised by solvent evaporation using a mixture Hexane: EtOAc

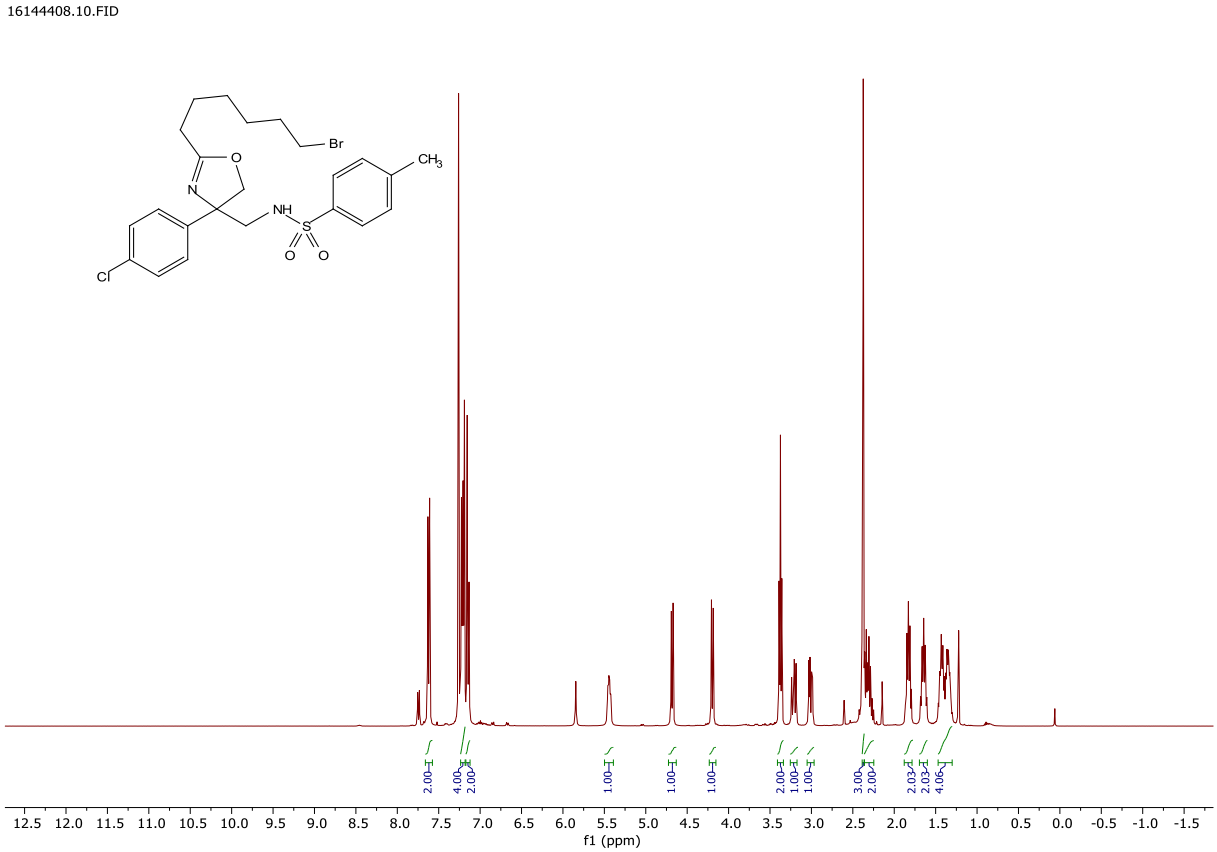
Experimental

Single crystals of $C_{23}H_{29}BrN_2O_3S$ were A suitable crystal was selected on a D8V_Mo diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

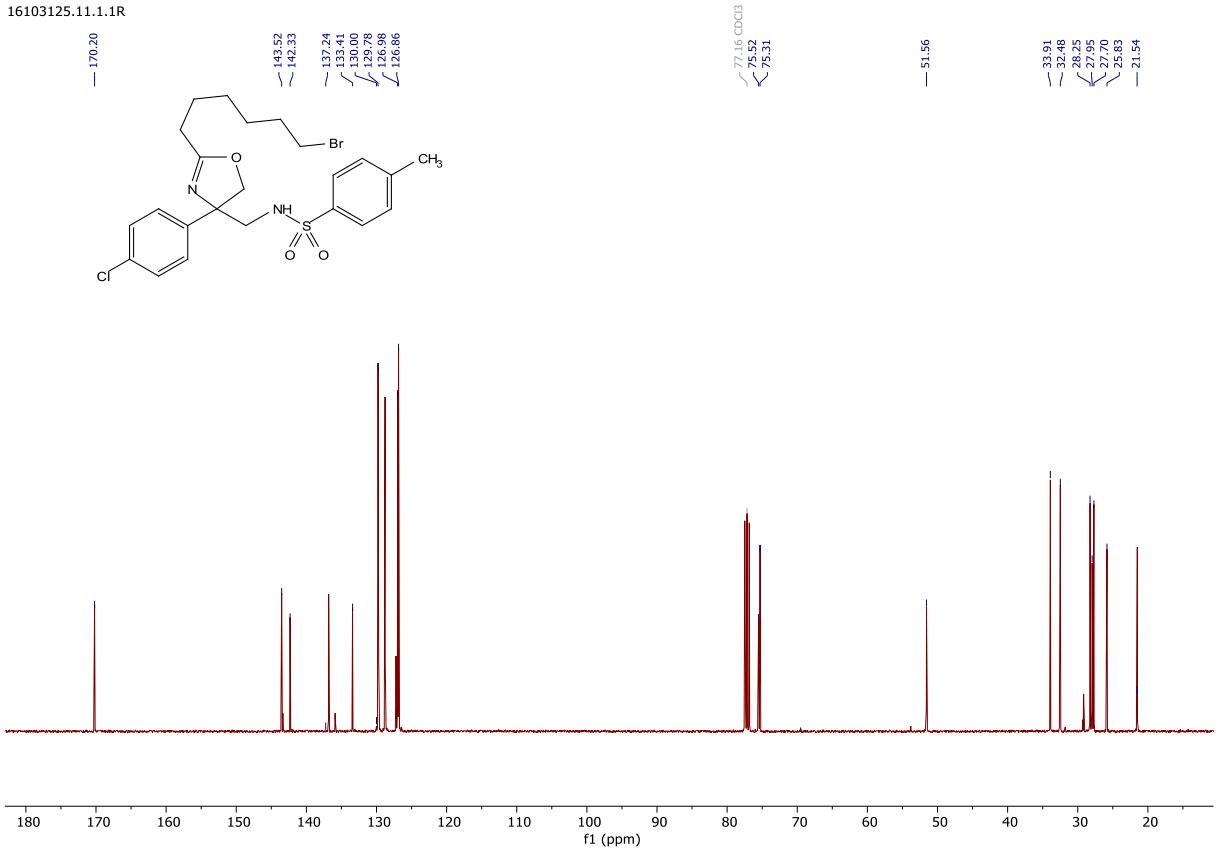
1) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2) Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
3) Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data for $C_{23}H_{29}BrN_2O_3S$ (M =493.45 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 12.7711(8) Å, b = 11.4910(7) Å, c = 16.0665(10) Å, β = 101.628(2)°, V = 2309.4(2) Å^3, Z = 4, T = 120 K, μ(MoKα) = 1.897 mm^{-1}, $Dcalc$ = 1.419 g/cm^3, 58322 reflections measured (4.39° ≤ 2Θ ≤ 65.146°), 8408 unique (R_{int} = 0.0386, R_{sigma} = 0.0274) which were used in all calculations. The final R_1 was 0.0306 (I > 2σ(I)) and wR_2 was 0.0844 (all data).

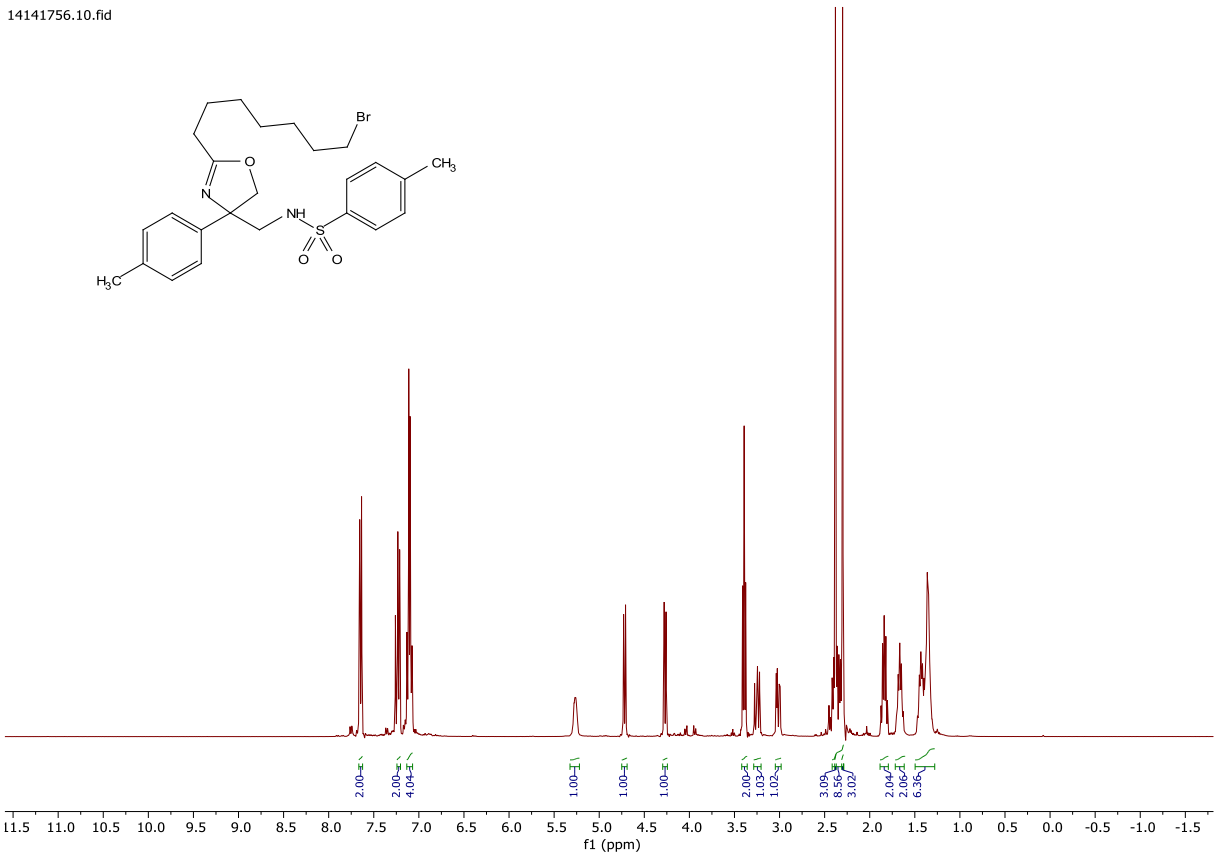
Compound 2-207 ^{1}H NMR (400 MHz, $CDCl_3$)



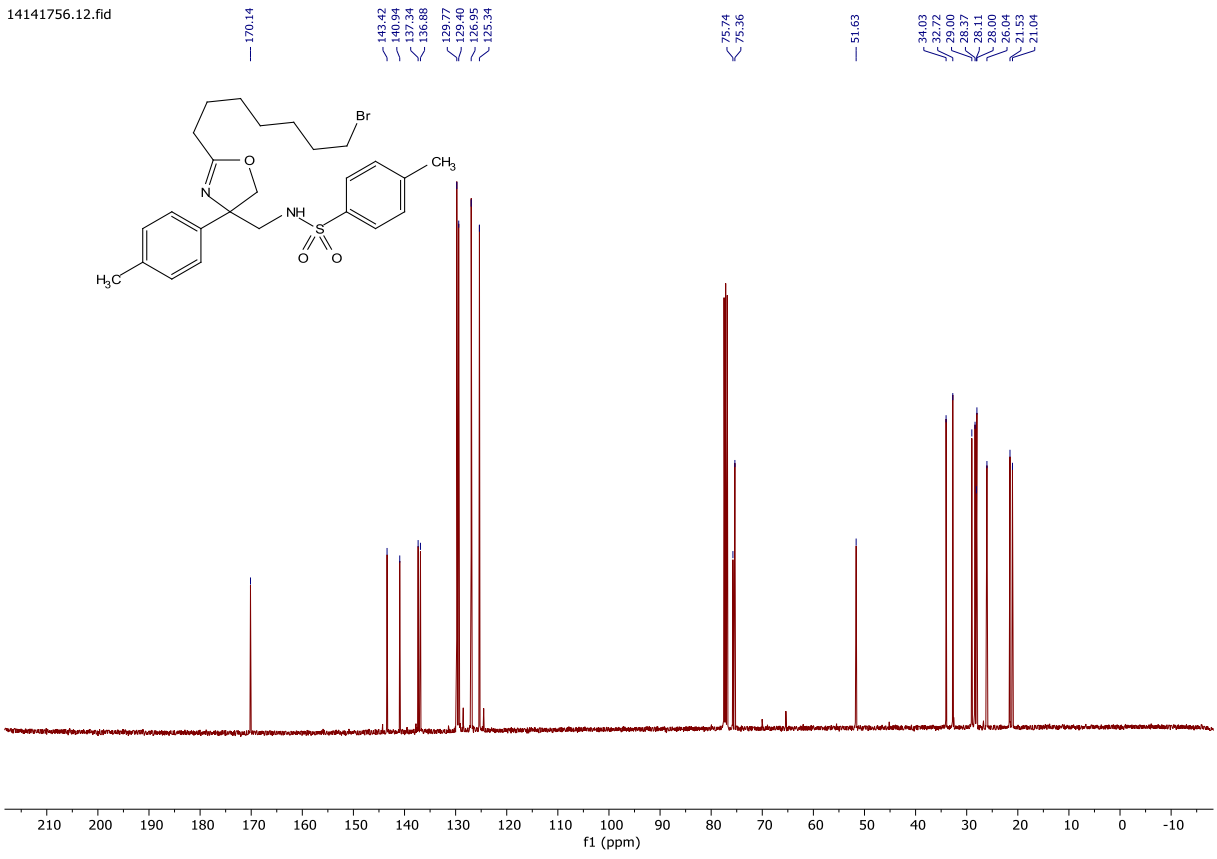
Compound **2-207** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



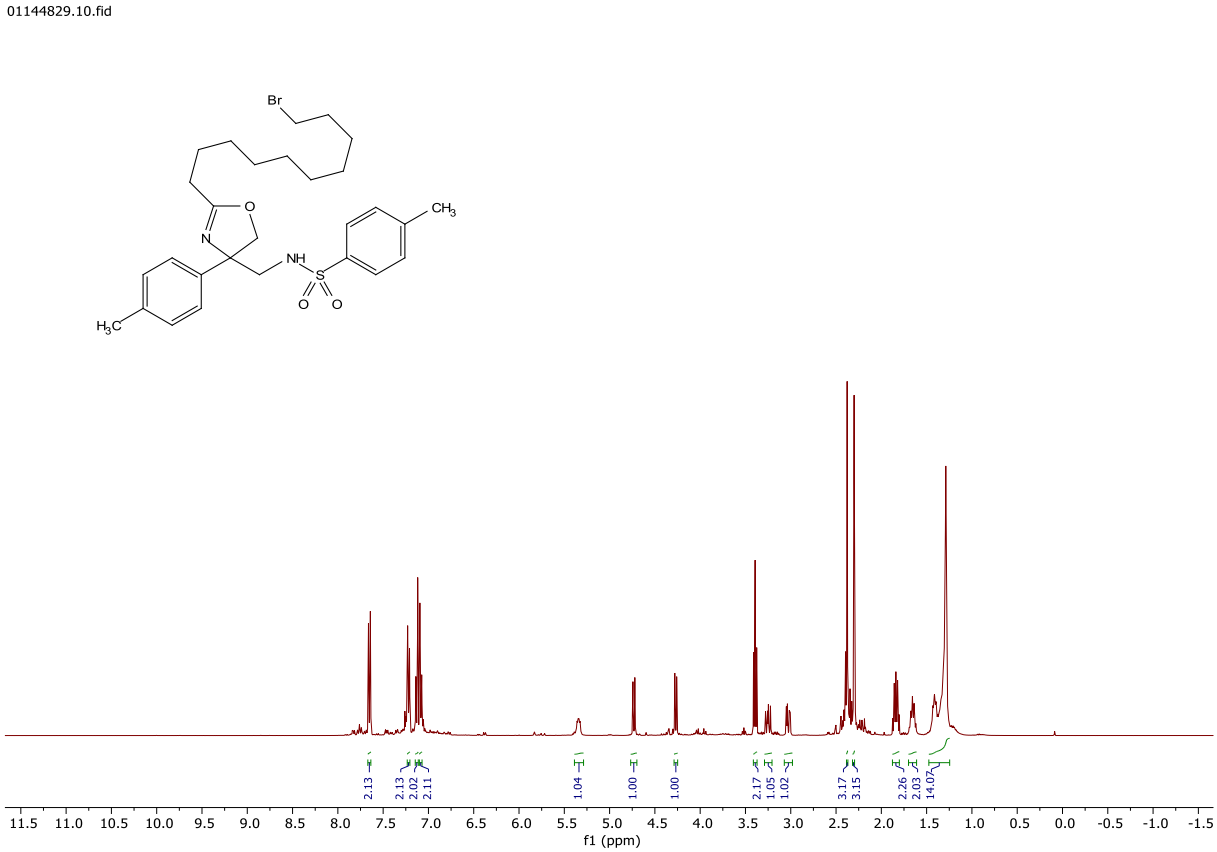
Compound 2-209 ^{1}H NMR (400 MHz, $CDCl_3$)



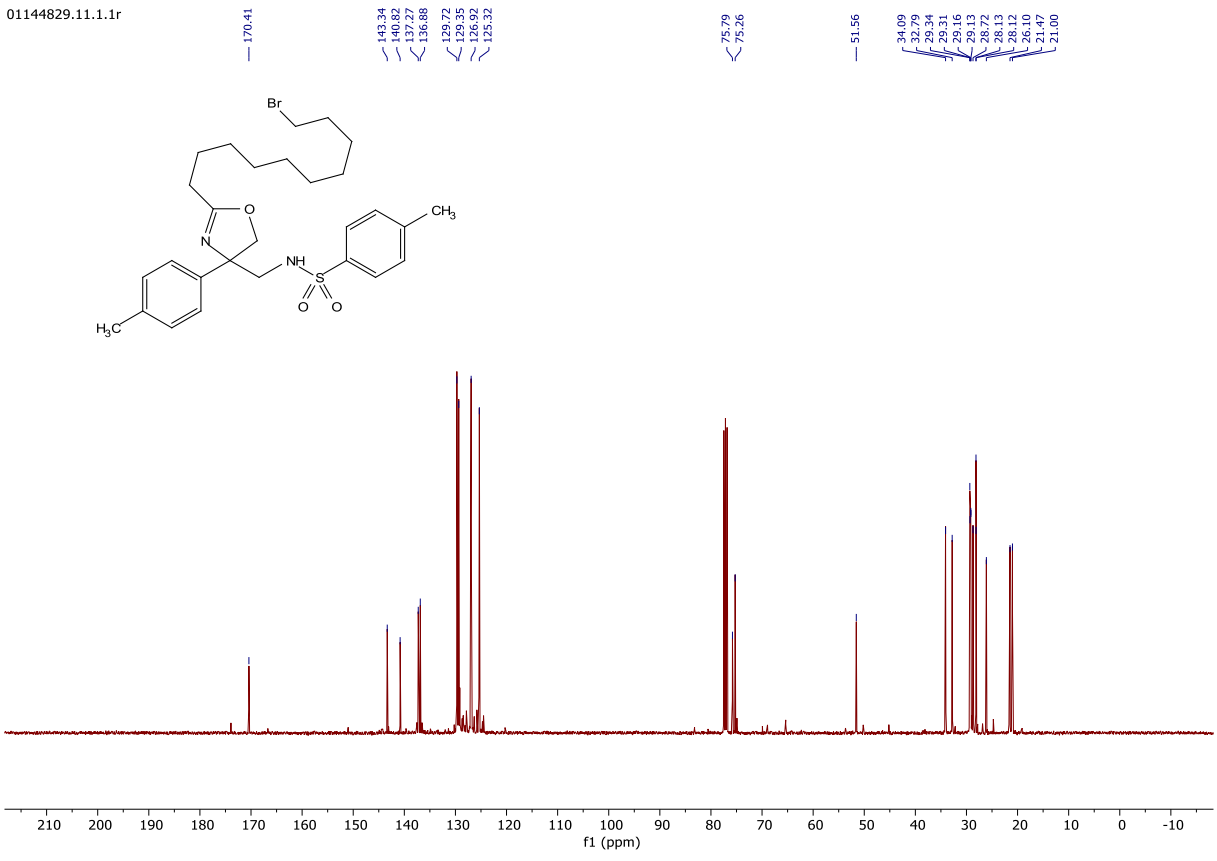
Compound **2-209** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



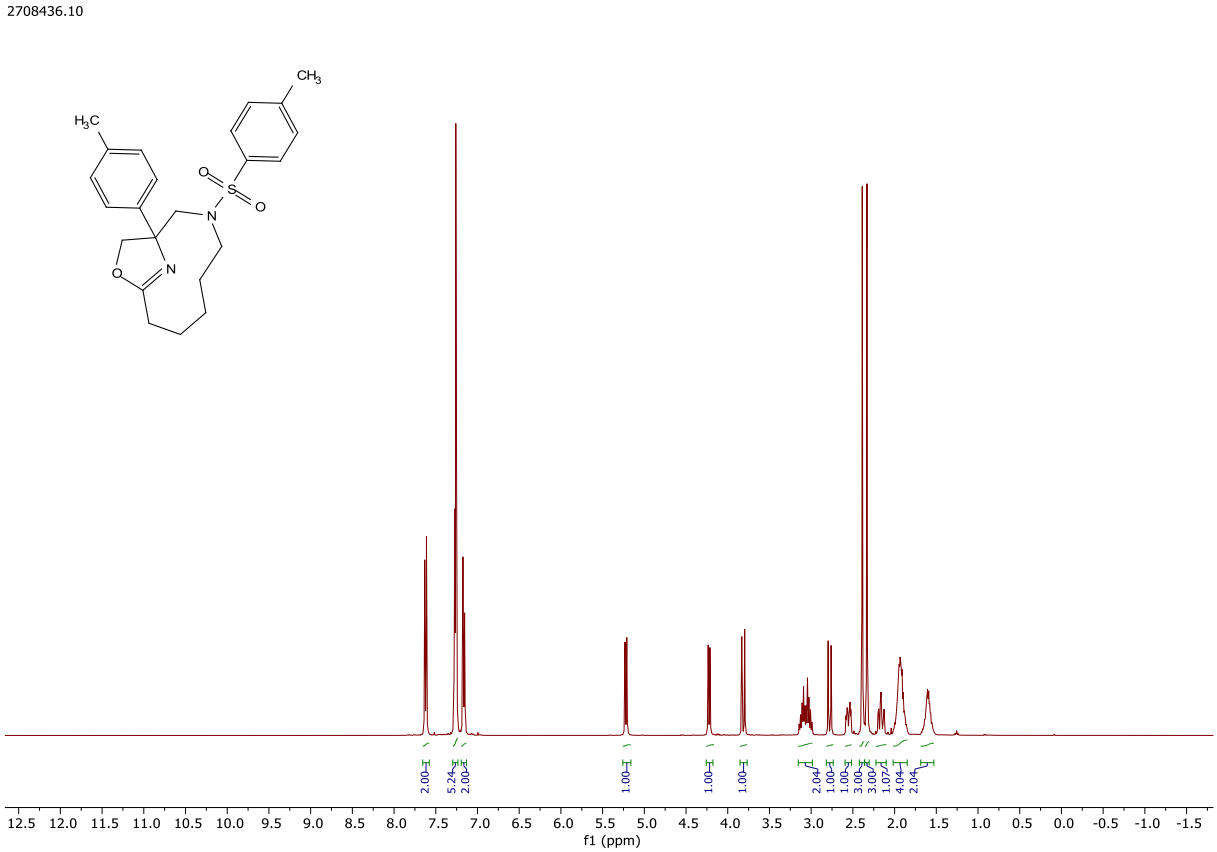
Compound 2-210 ^{1}H NMR (400 MHz, $CDCl_3$)



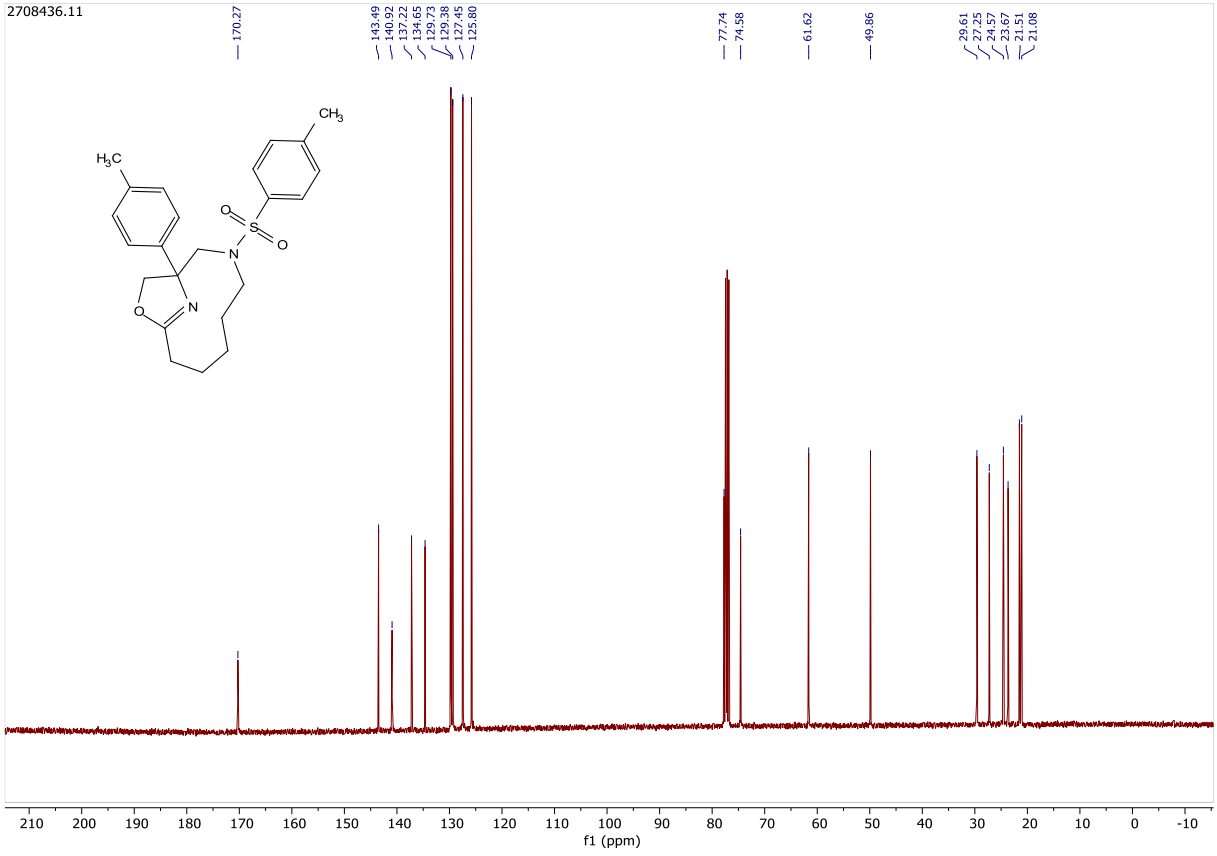
Compound **2-210** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



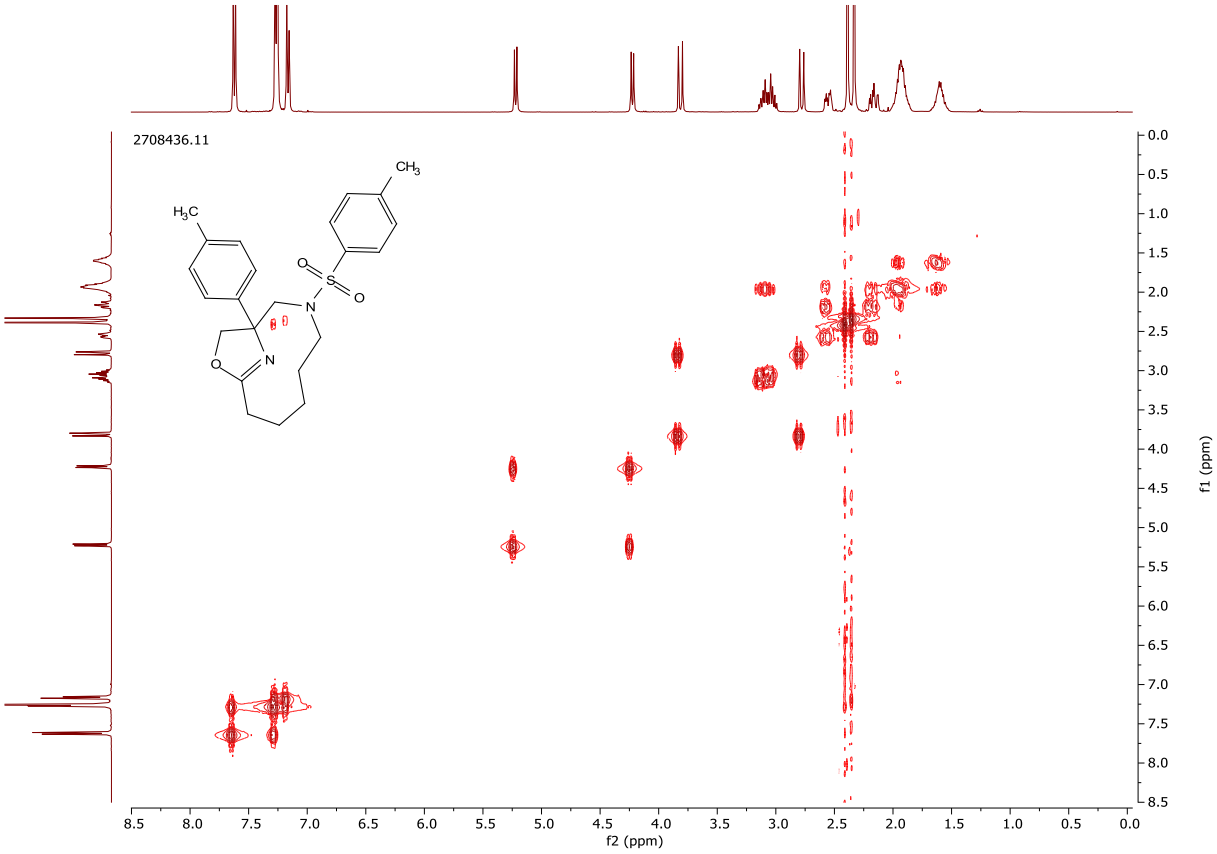
Compound 2-211 ^{1}H NMR (400 MHz, $CDCl_3$)



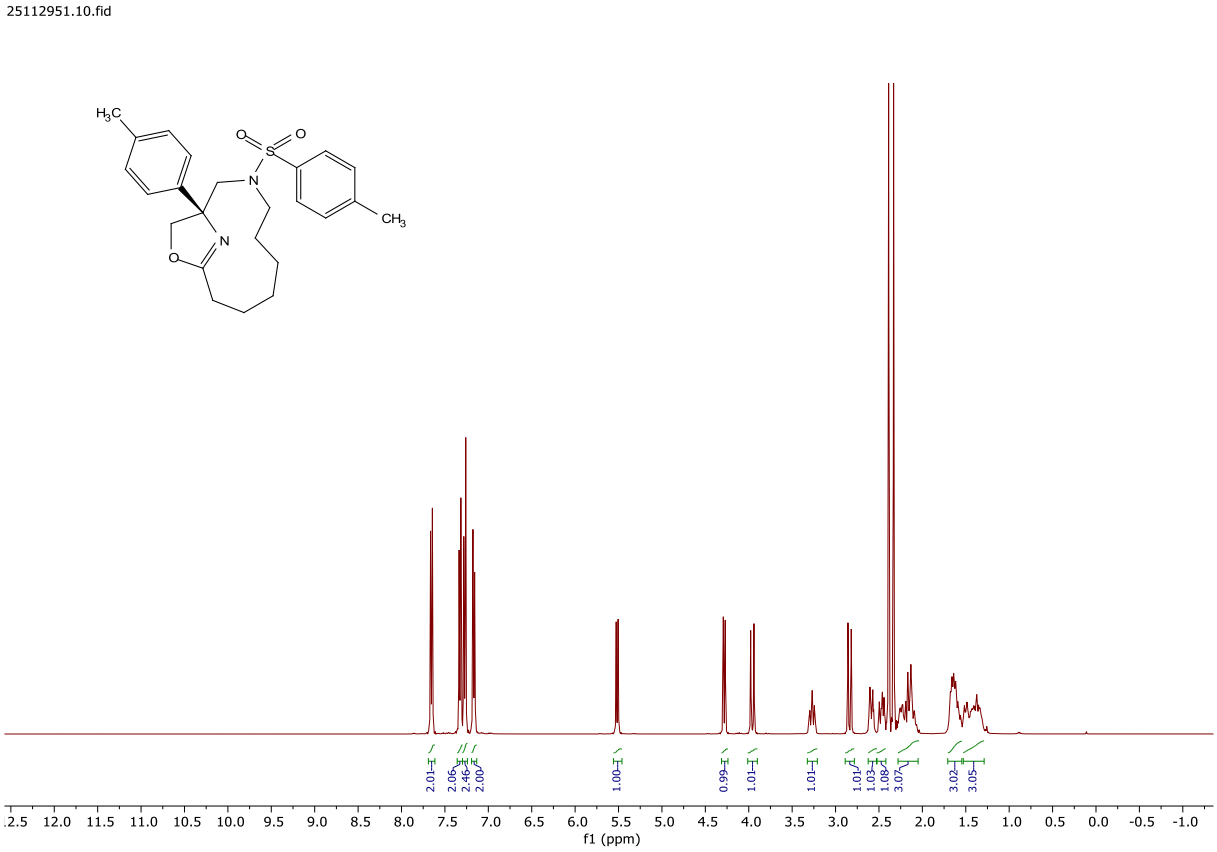
Compound **2-211** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



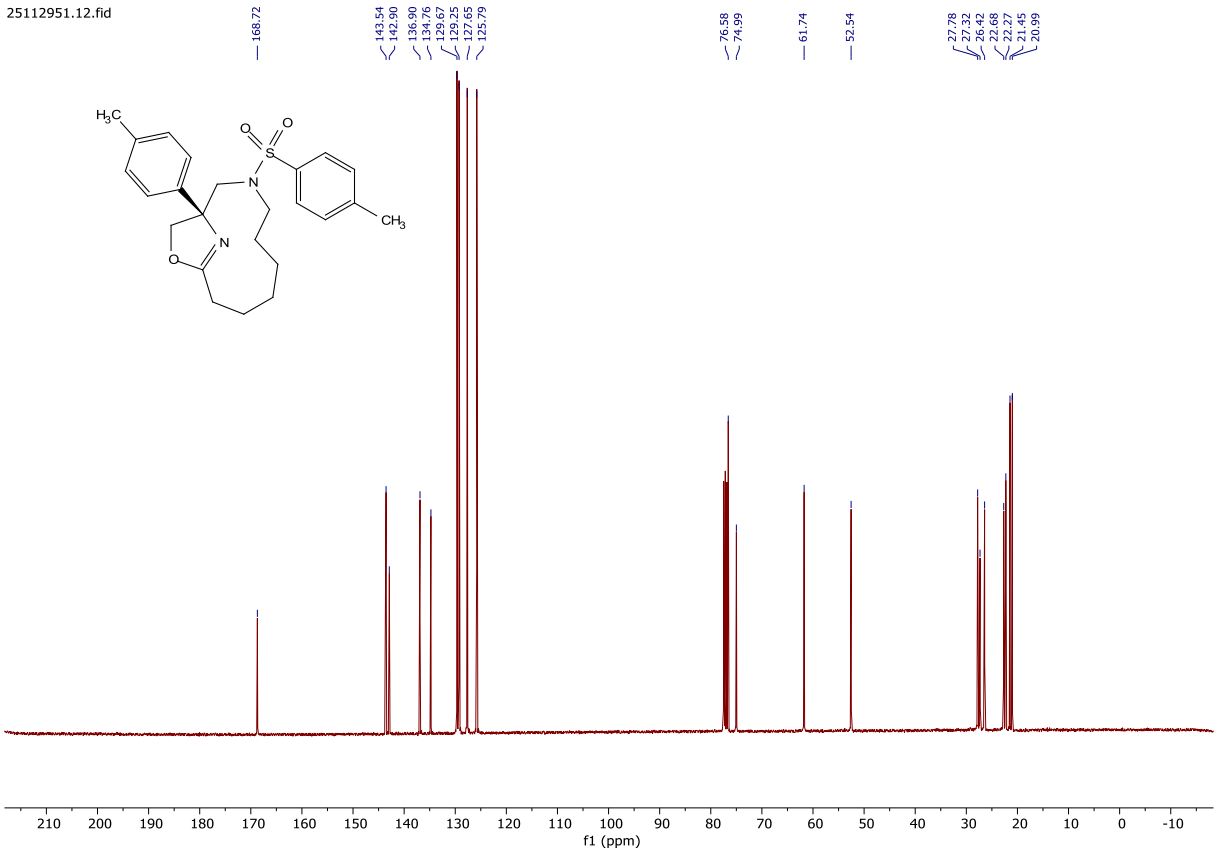
Compound 2-211, COSY (400 MHz, $CDCl_3$)



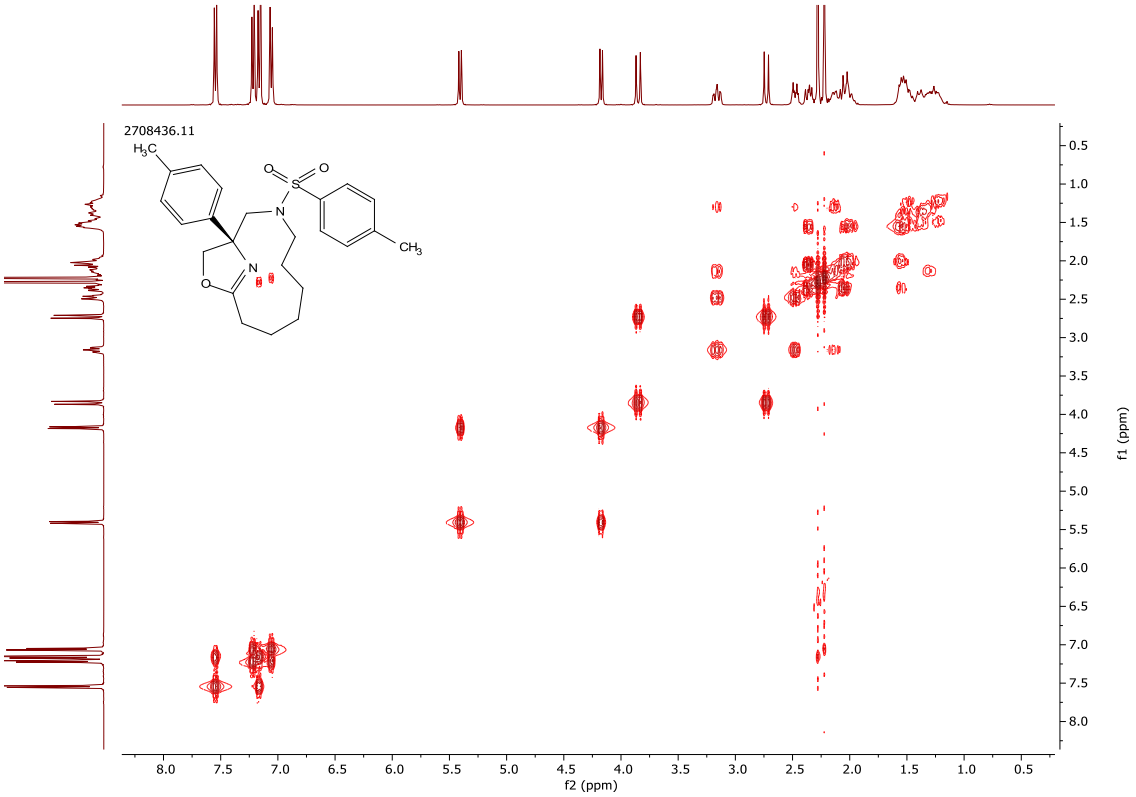
Compound 2-212 ^{1}H NMR (400 MHz, $CDCl_3$)



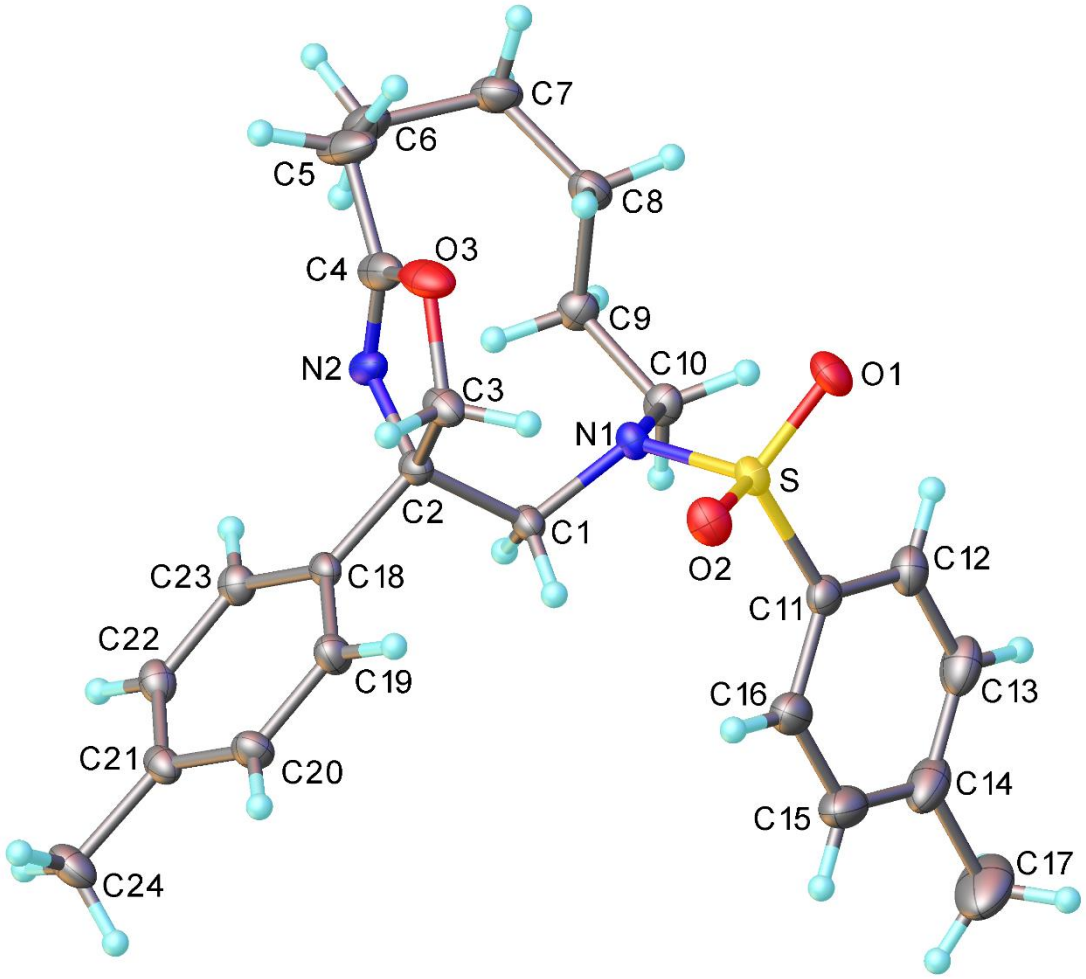
Compound **2-212** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



Compound 2-212 COSY (400 MHz, $CDCl_3$)



Compound 2-212 X-ray structure



Atomic displacement ellipsoids are drawn at the 50% probability level.

Compound 14-2 was crystallised by solvent evaporation using a mixture Hexane: EtOAc

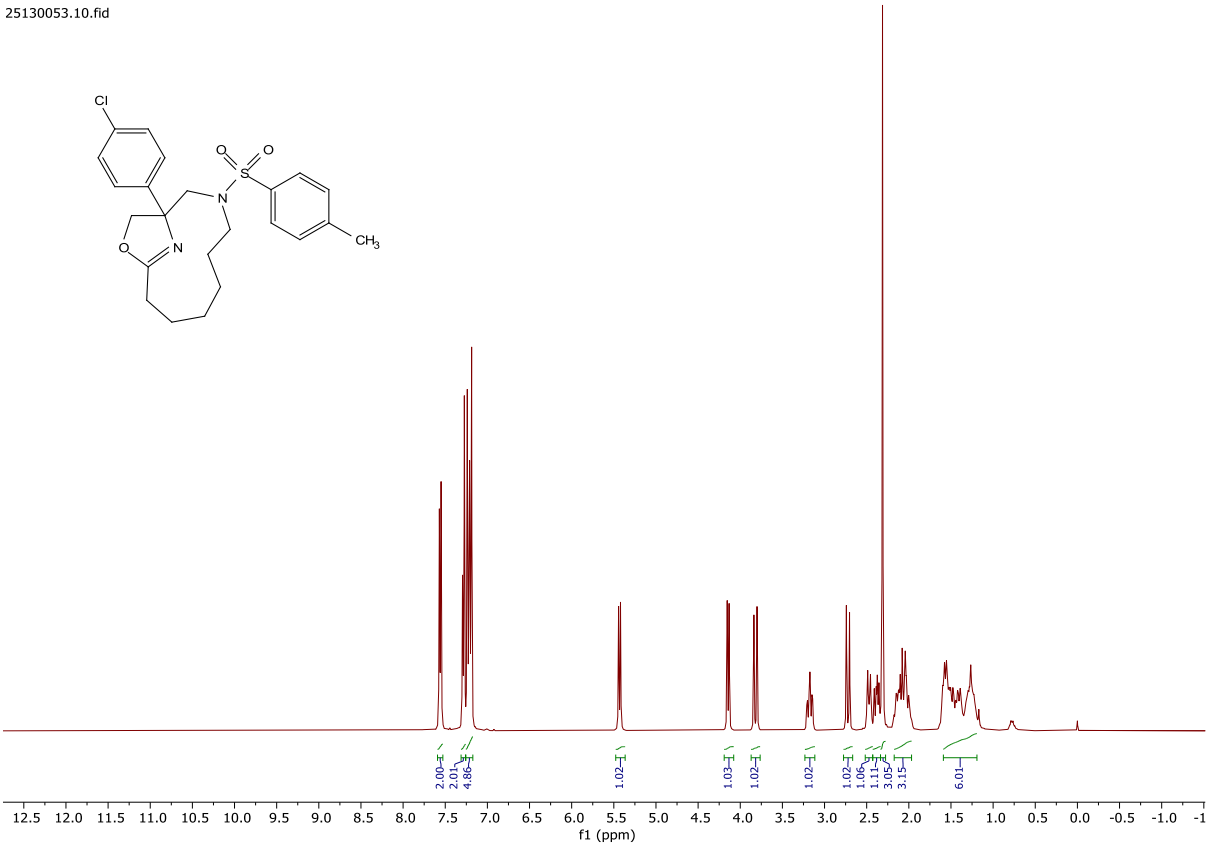
Experimental

Single crystals of $C_{24}H_{30}N_2O_3S$ were A suitable crystal was selected on a D8V_Mo diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

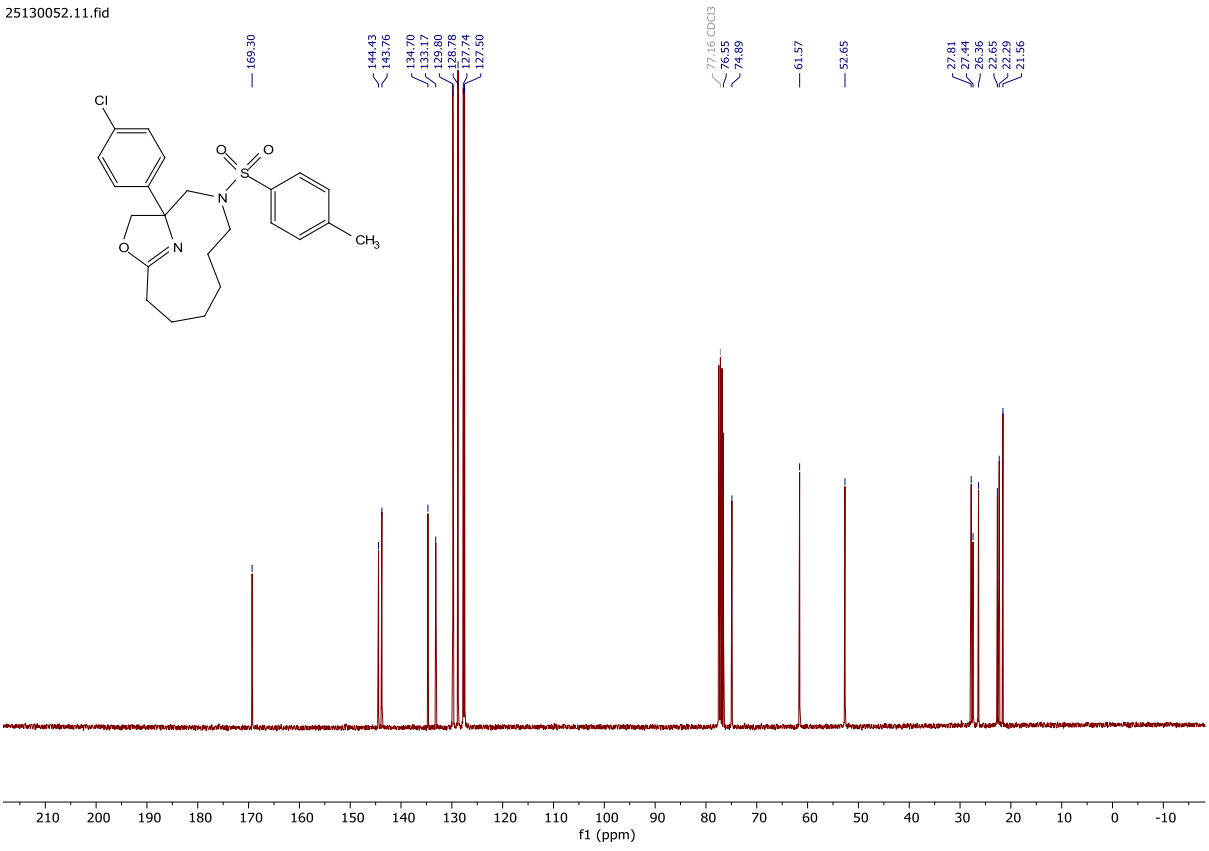
1) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2) Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
3) Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data for $C_{24}H_{30}N_2O_3S$ (*M* =426.56 g/mol): monoclinic, space group $P2_1/n$ (no. 14), *a* = 10.5538(7) Å, *b* = 21.7626(14) Å, *c* = 10.9319(7) Å, *β* = 116.908(2)°, *V* = 2239.0(3) Å^3, *Z* = 4, *T* = 120 K, μ(MoKα) = 0.172 mm^{-1}, *Dcalc* = 1.265 g/cm^3, 49376 reflections measured (4.452° ≤ 2Θ ≤ 59.99°), 6522 unique (R_{int} = 0.0418, R_{sigma} = 0.0287) which were used in all calculations. The final R_1 was 0.0399 (I > 2σ(I)) and wR_2 was 0.1099 (all data).

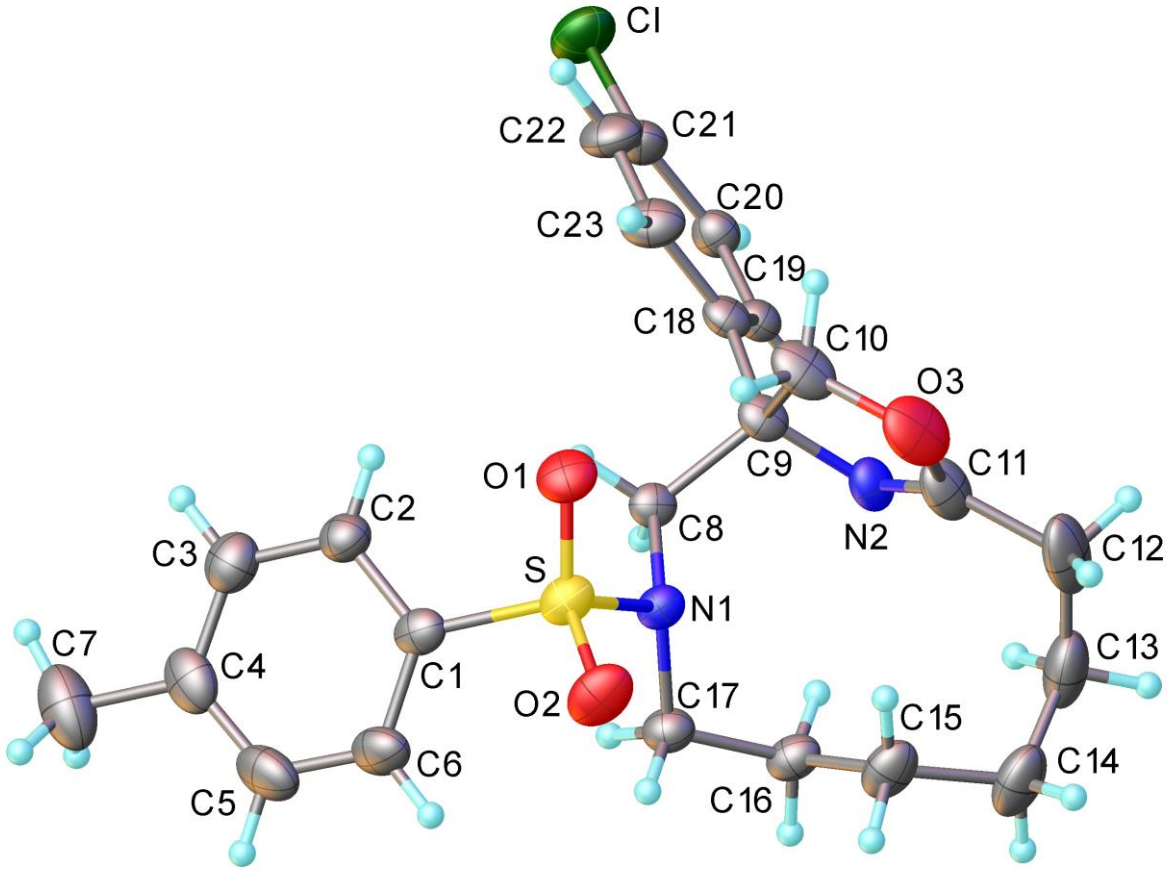
Compound 2-213 ^{1}H NMR (400 MHz, $CDCl_3$)



Compound **2-213** ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)



Compound 2-213 X-ray structure



Atomic displacement ellipsoids are drawn at the 50% probability level.

Compound 14-3 was crystallised by solvent evaporation using a mixture Hexane: EtOAc

Experimental

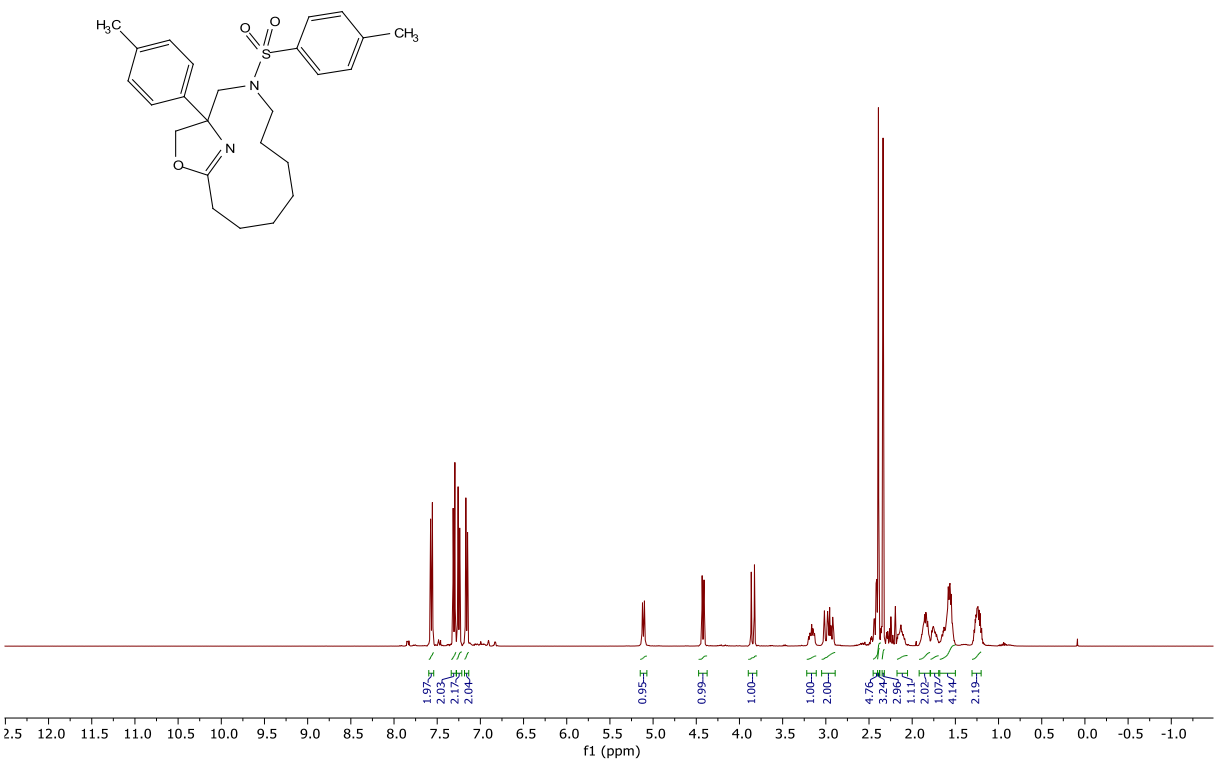
Single crystals of $C_{23}H_{27}ClN_2O_3S$ were A suitable crystal was selected on a D8V_Mo diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2) Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
3) Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data for $C_{23}H_{27}ClN_2O_3S$ (M =446.97 g/mol): triclinic, space group P-1 (no. 2), a = 5.8929(3) Å, b = 17.3978(9) Å, c = 21.6160(12) Å, α = 89.719(2)°, β = 89.096(2)°, γ = 81.028(2)°, V = 2188.8(2) Å^3, Z = 4, T = 120 K, μ(MoKα) = 0.298 mm^{-1}, *Dcalc* = 1.356 g/cm^3, 34462 reflections measured (4.448° ≤ 2Θ ≤ 50.052°), 7680 unique (R_{int} = 0.0507, R_{sigma} = 0.0566) which were used in all calculations. The final R_1 was 0.0648 (I > 2σ(I)) and wR_2 was 0.1636 (all data).

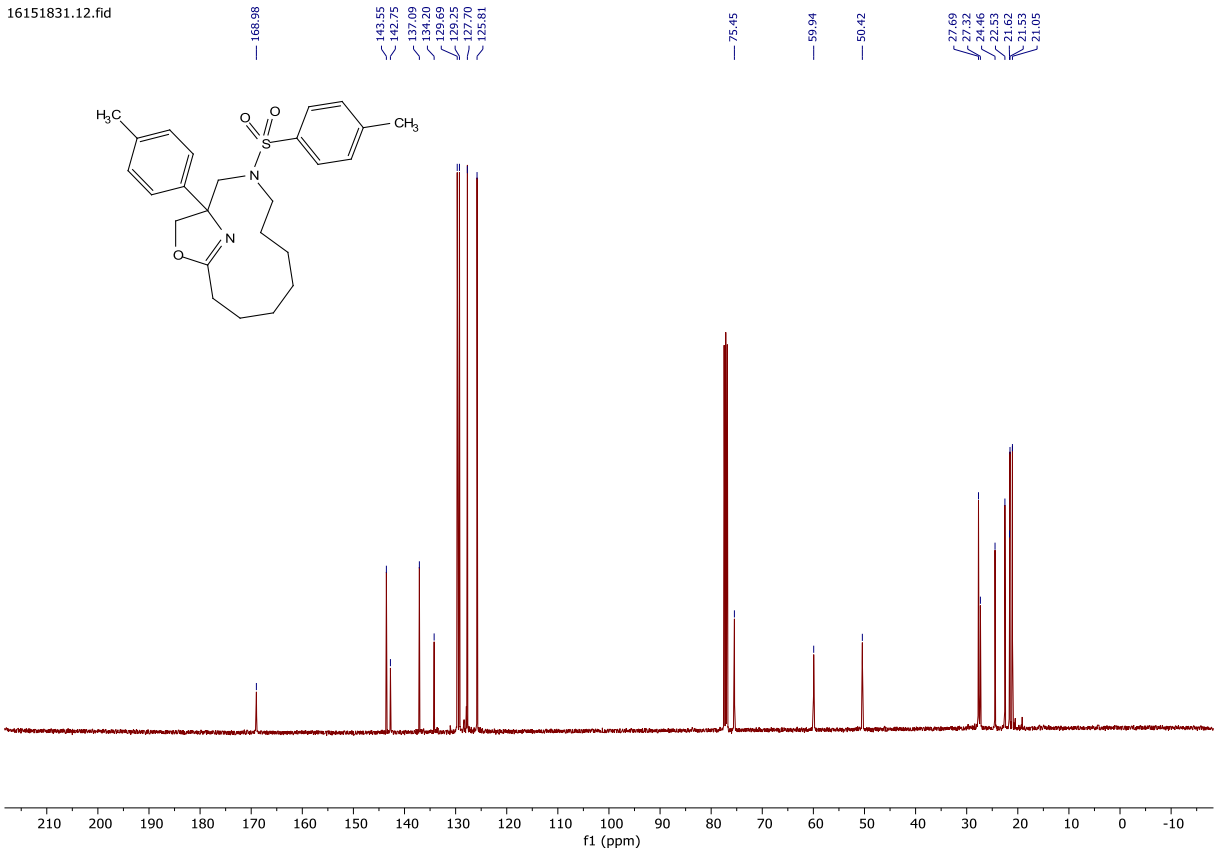
Compound 2-214 ^{1}H NMR (400 MHz, $CDCl_3$)

17092709.10.fid

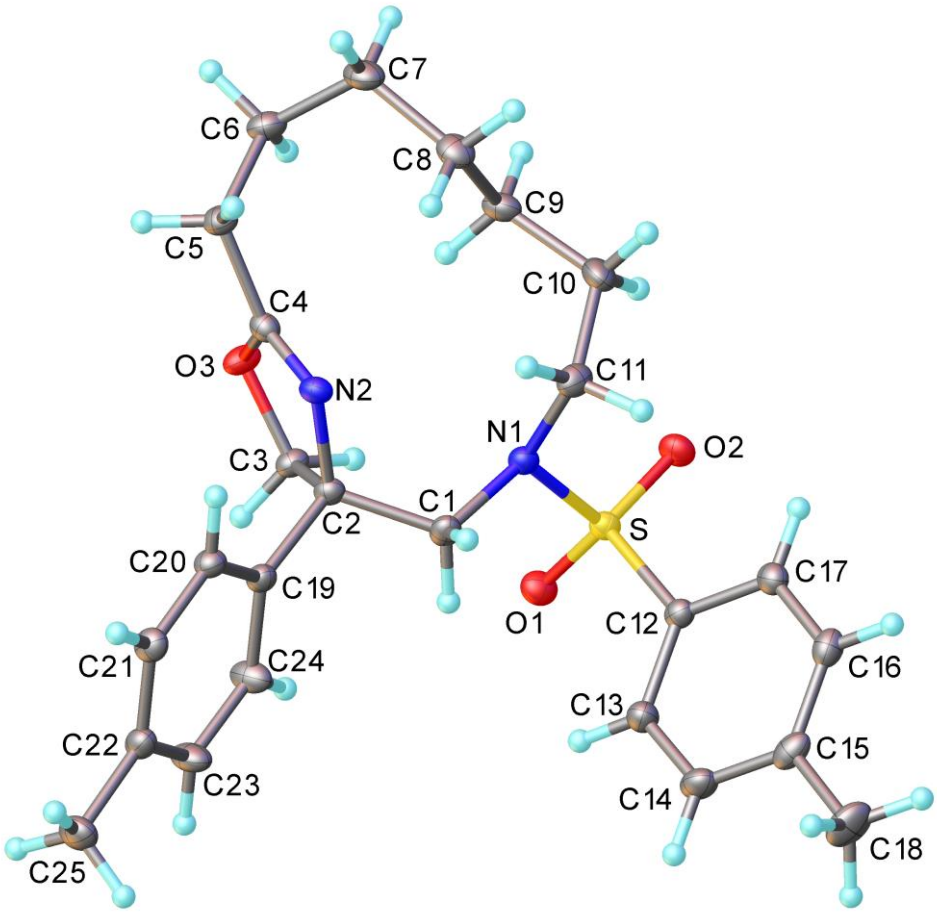


Compound **2-214** ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$)

16151831.12.fid



Compound 2-214 X-ray structure



Atomic displacement ellipsoids are drawn at the 50% probability level.

Compound 14-4 was crystallised by solvent evaporation using a mixture Hexane: EtOAc

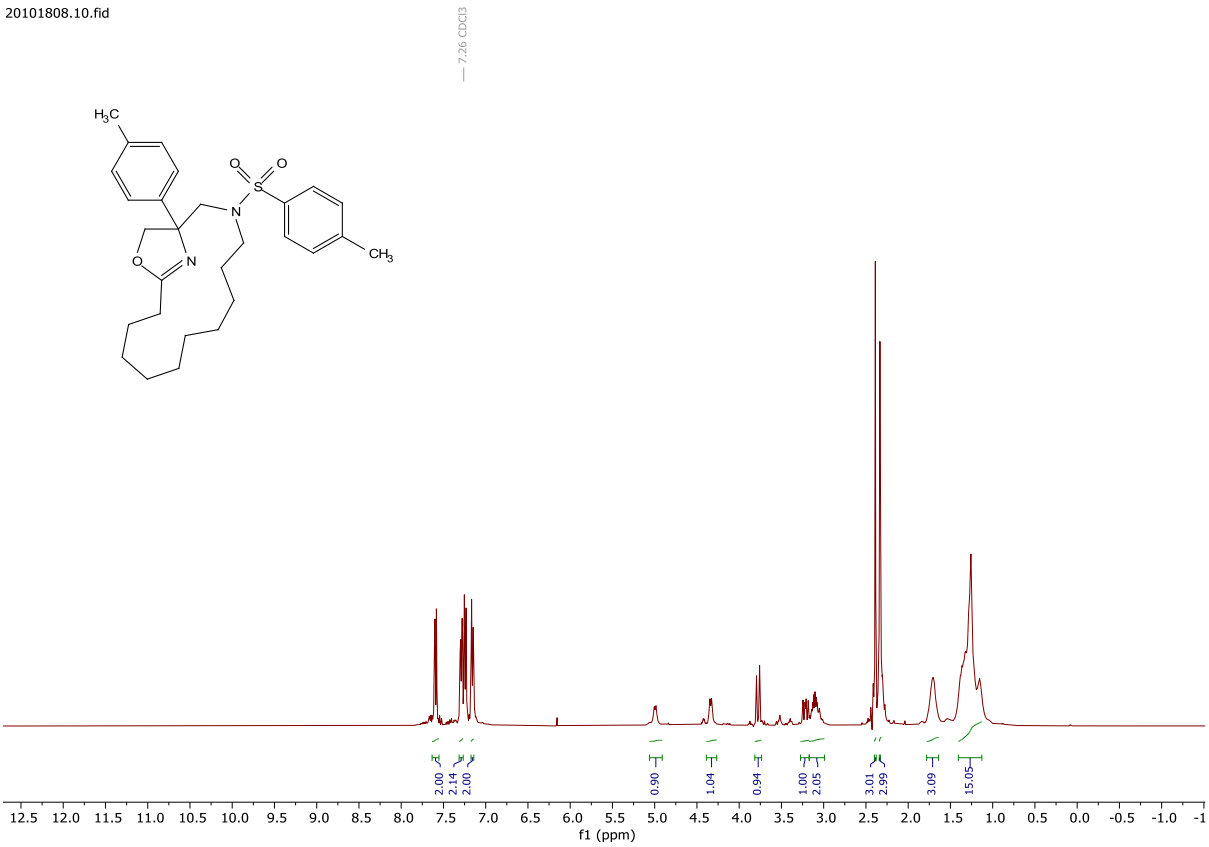
Experimental

Single crystals of $C_{25}H_{32}N_2O_3S$ were A suitable crystal was selected on a D8V_Mo diffractometer. The crystal was kept at 120 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimisation.

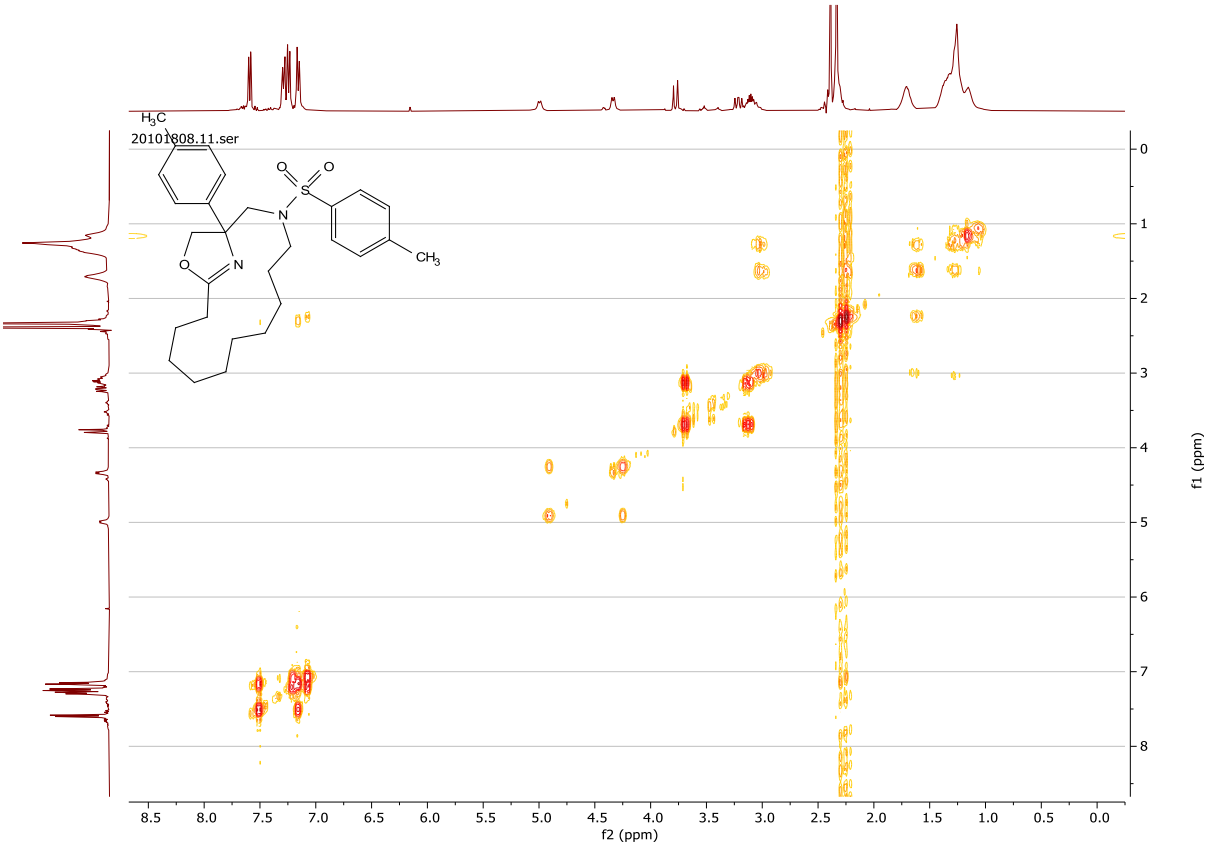
1) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2) Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
3) Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal Data for $C_{25}H_{32}N_2O_3S$ (M =440.58 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 10.5408(7) Å, b = 11.4873(7) Å, c = 19.3042(13) Å, β = 102.914(2)°, V = 2278.3(3) Å^3, Z = 4, T = 120 K, μ(MoKα) = 0.171 mm^{-1}, *Dcalc* = 1.284 g/cm^3, 49671 reflections measured (4.33° ≤ 2Θ ≤ 60.254°), 6697 unique (R_{int} = 0.0431, R_{sigma} = 0.0318) which were used in all calculations. The final R_1 was 0.0396 (I > 2σ(I)) and wR_2 was 0.1044 (all data).

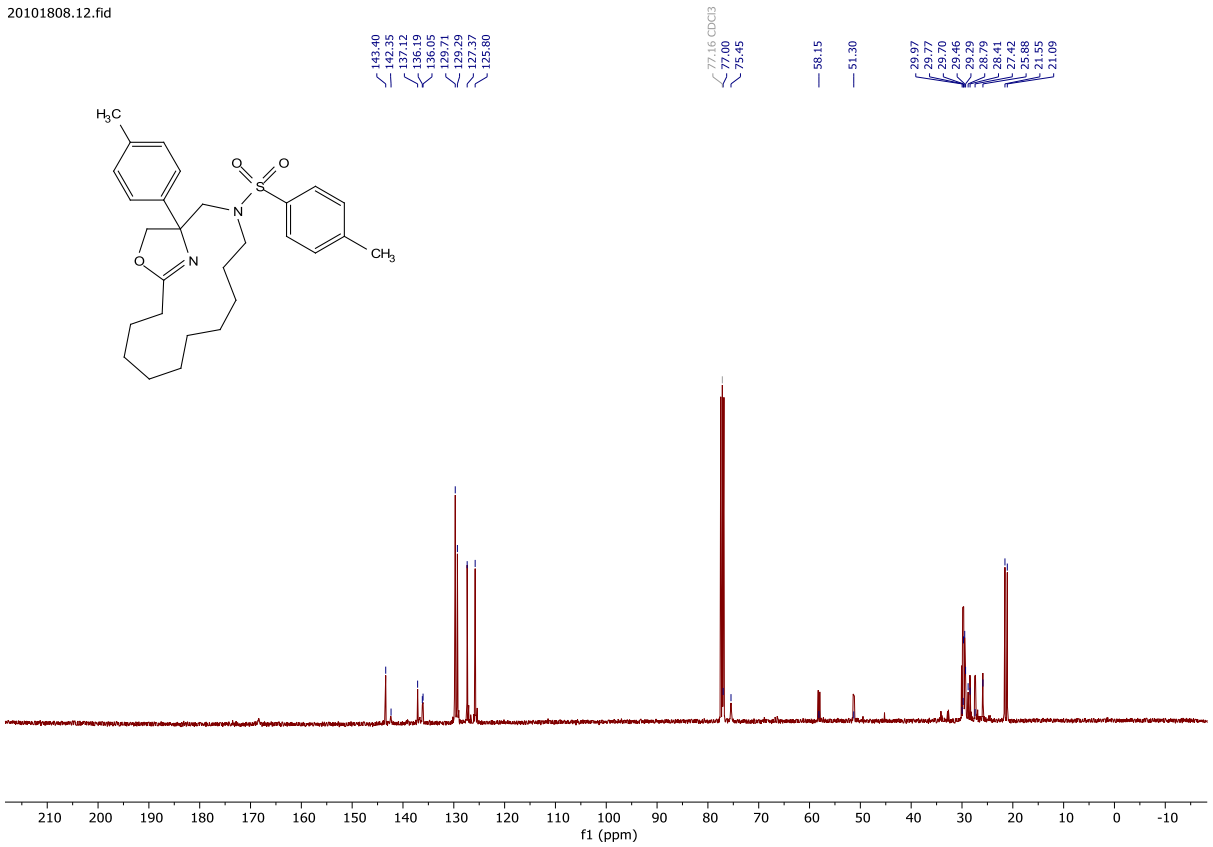
Compound 2-215 ^{1}H NMR (400 MHz, $CDCl_3$)



Compound 2-215 COSY (400 MHz, $CDCl_3$)



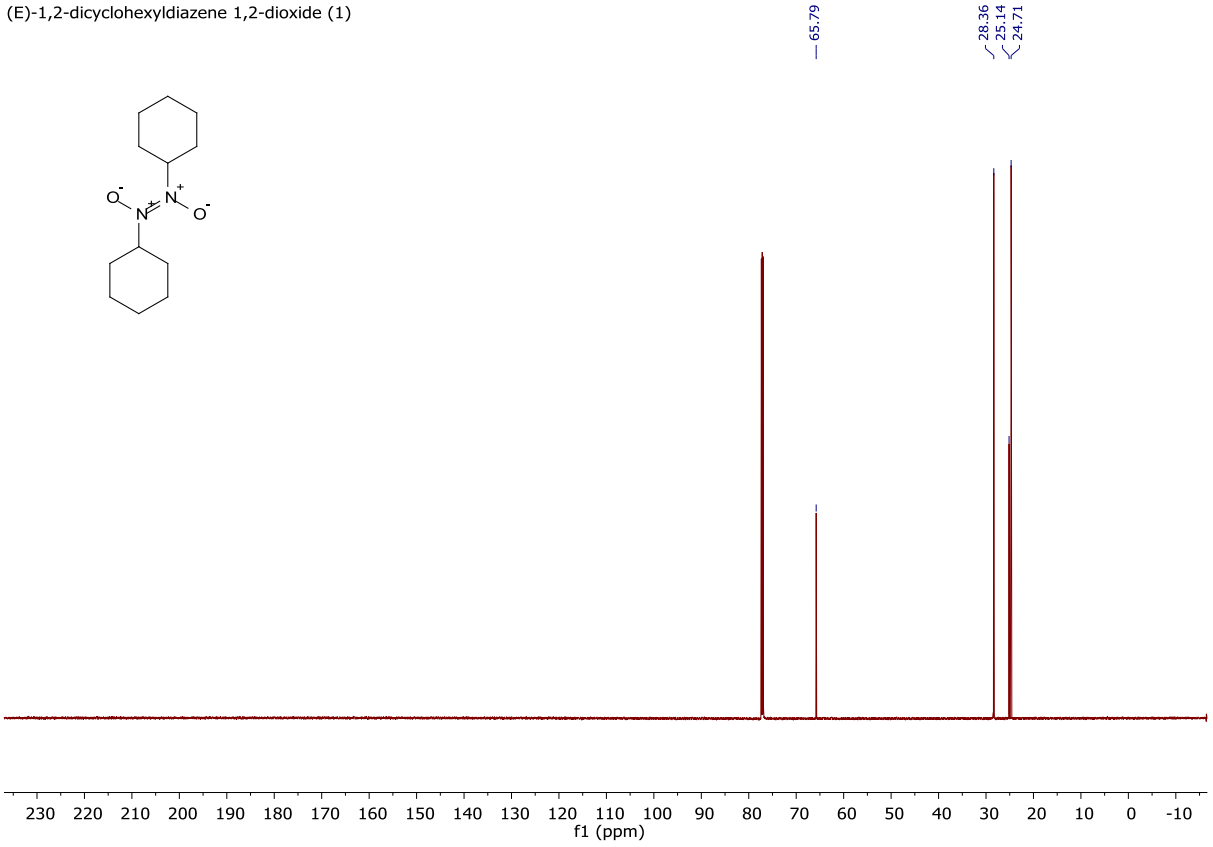
Compound 2-215 $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$)

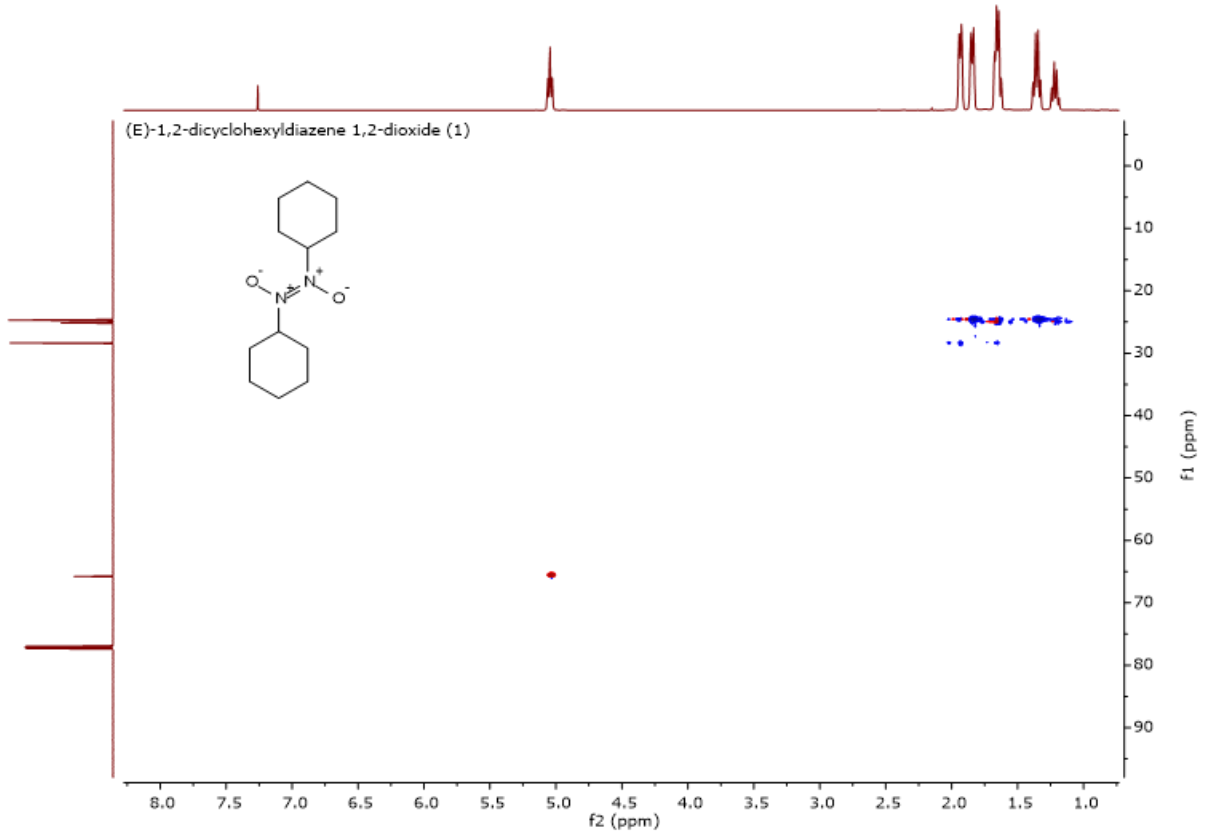


ica Acta, ***2007*** *90*, 1420−1438.

[7] K. Raja, Erum. A. Klumpp, Douglas, *Tetrahedron,* ***2011****, 67*, 4494−4497.

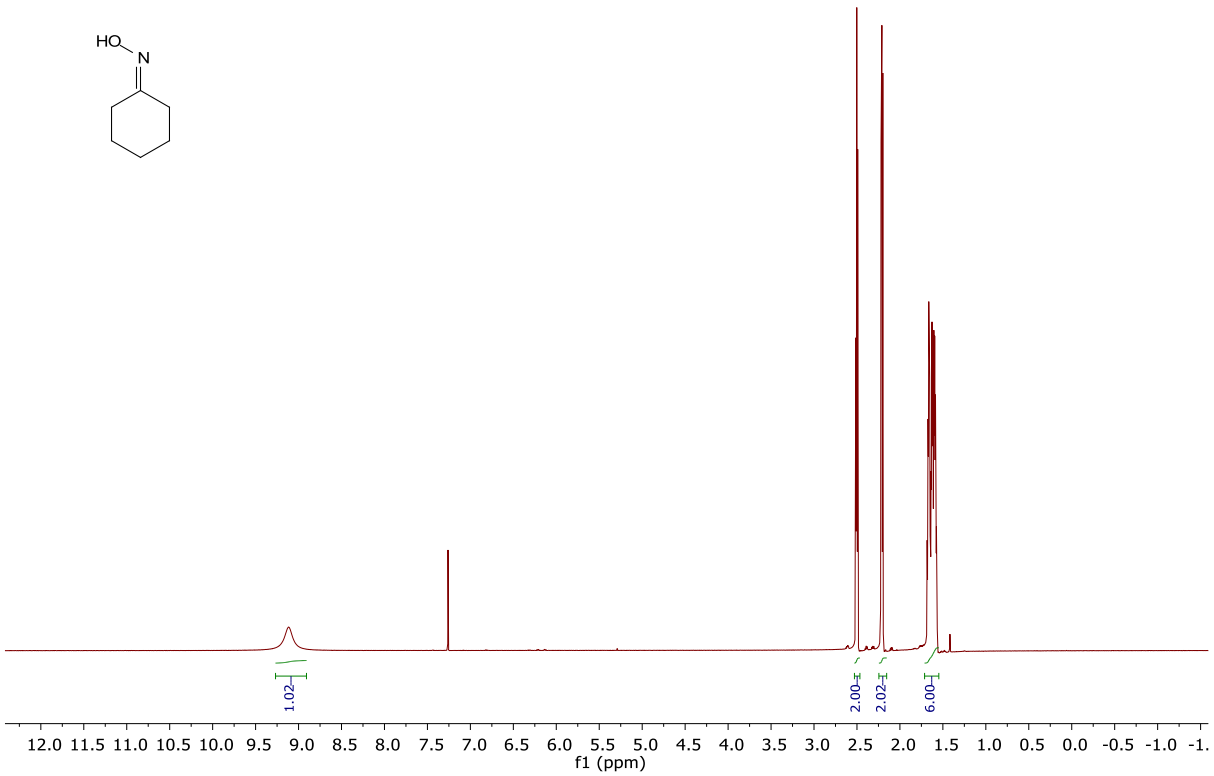
Compound **3-176** $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$)



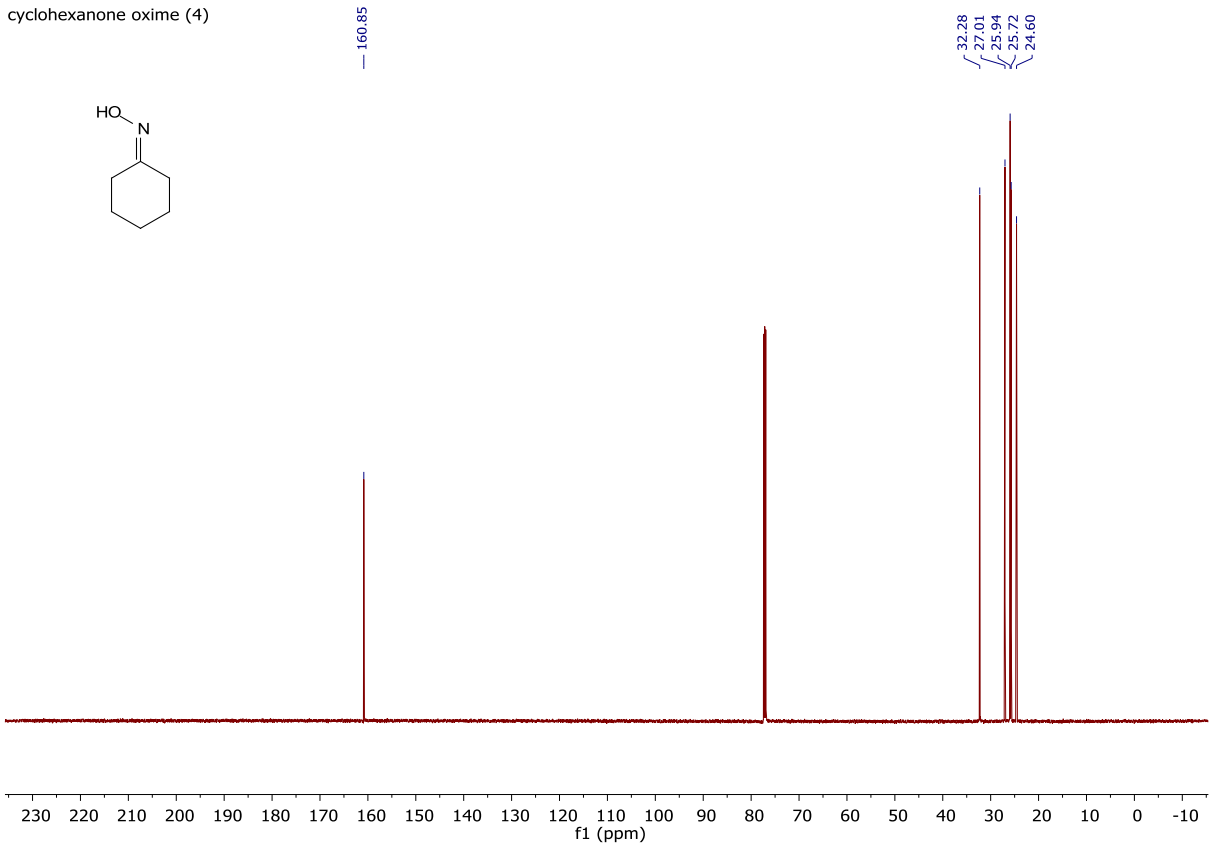


Compound 3-7 ^{1}H NMR (400 MHz, $CDCl_3$)

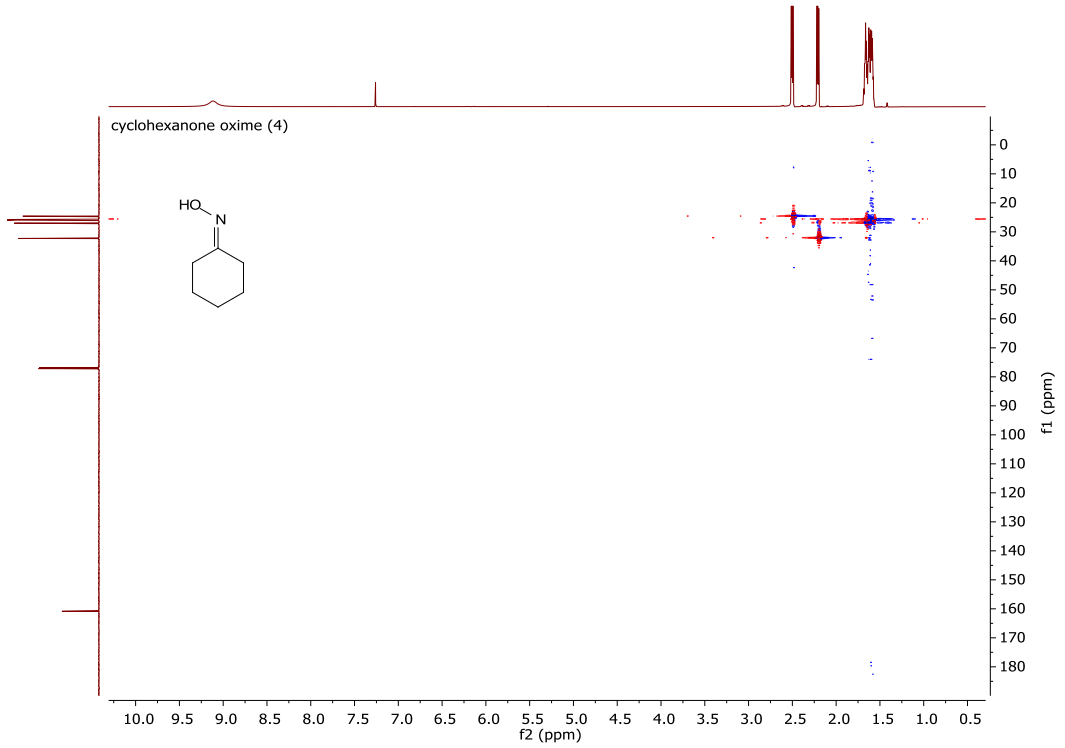
cyclohexanone oxime (4)



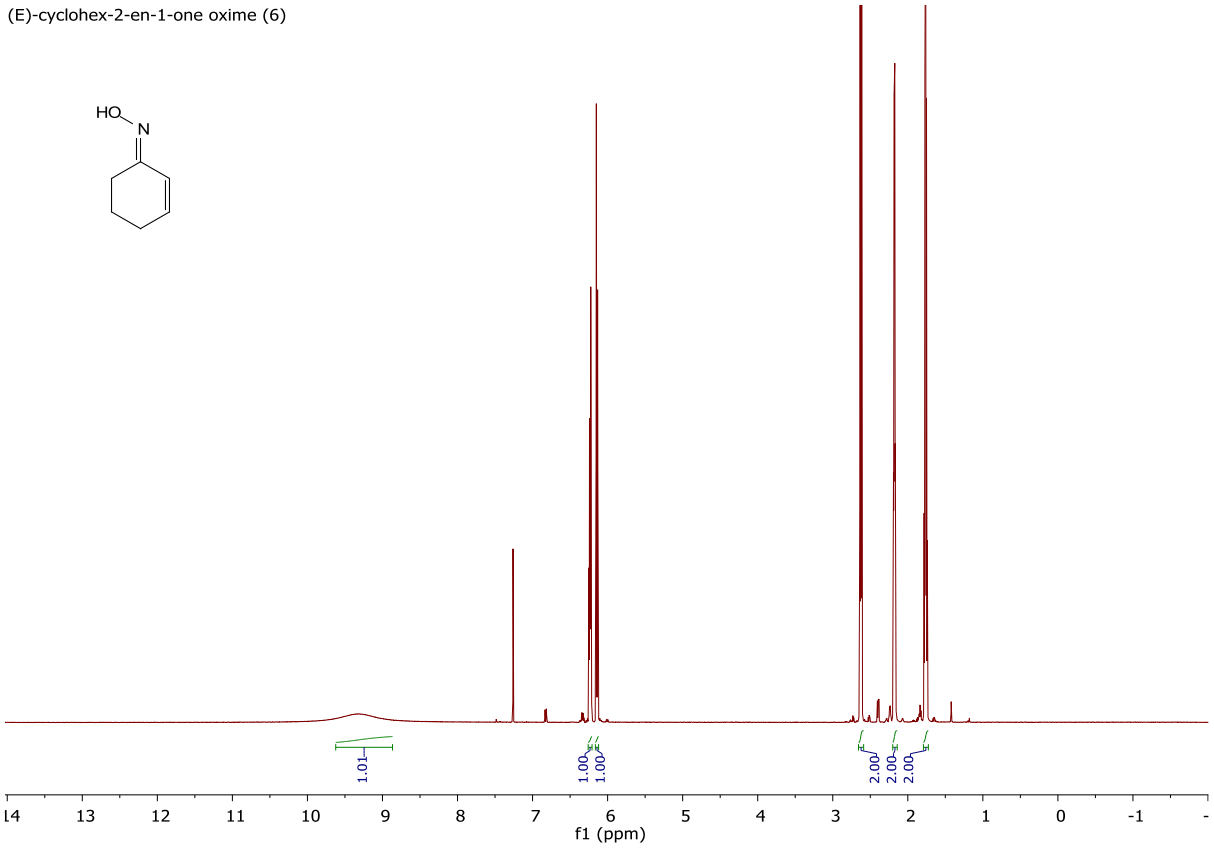
Compound **3-7** $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$)



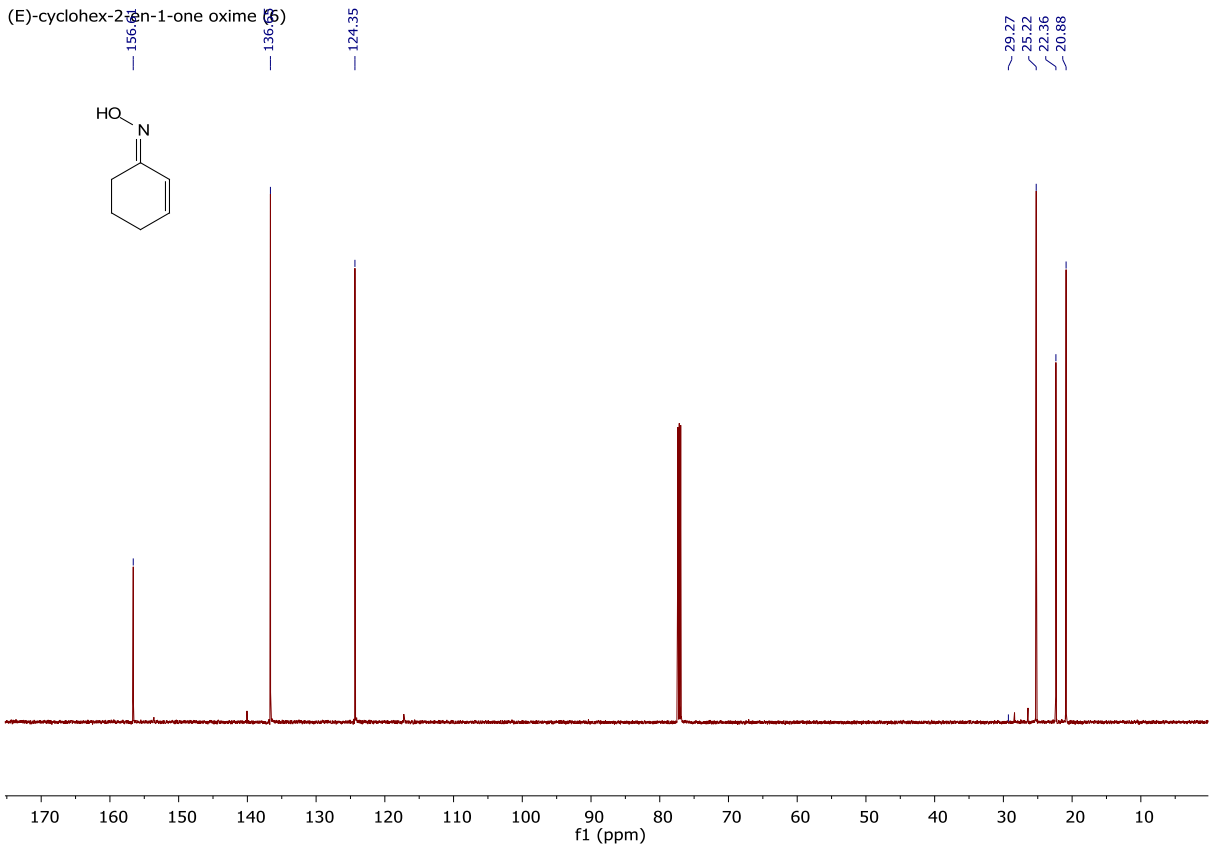
Compound 3-7 HSQC (600 MHz, $CDCl_3$)



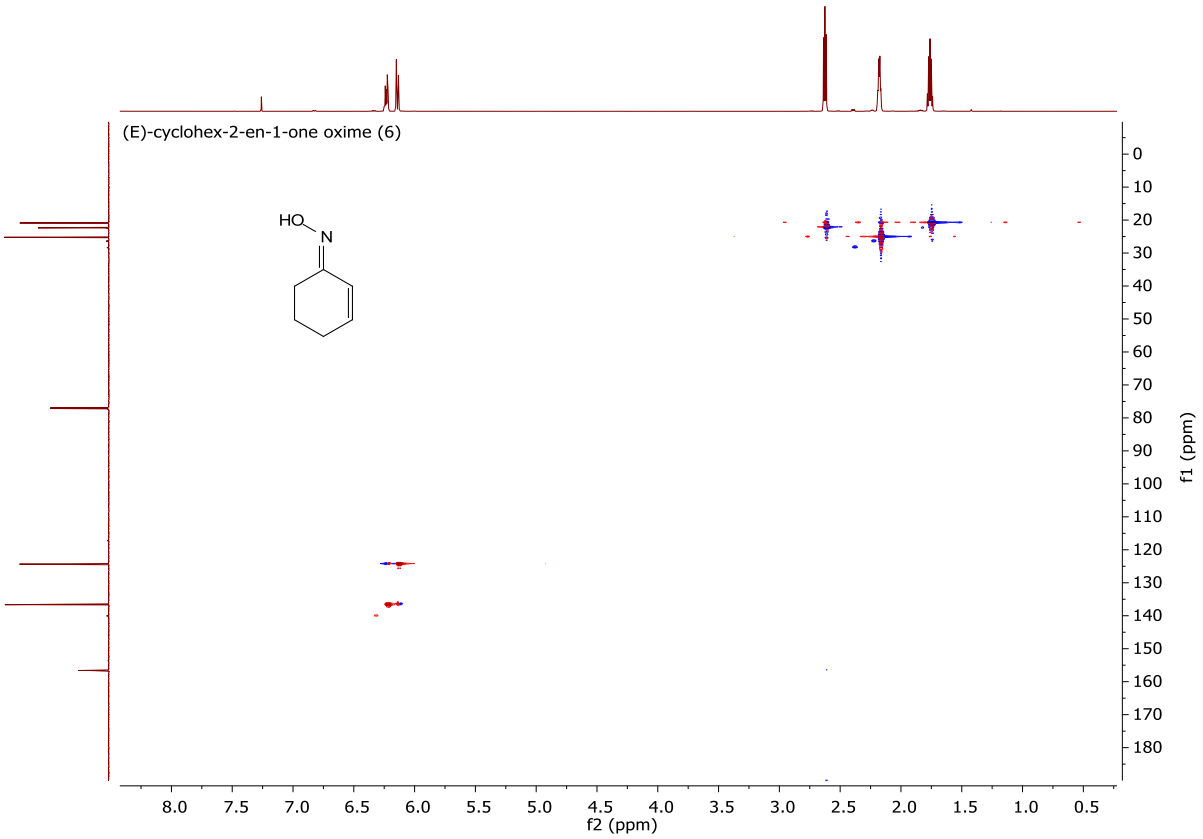
Compound 3-187a ^{1}H NMR (600 MHz, $CDCl_3$)



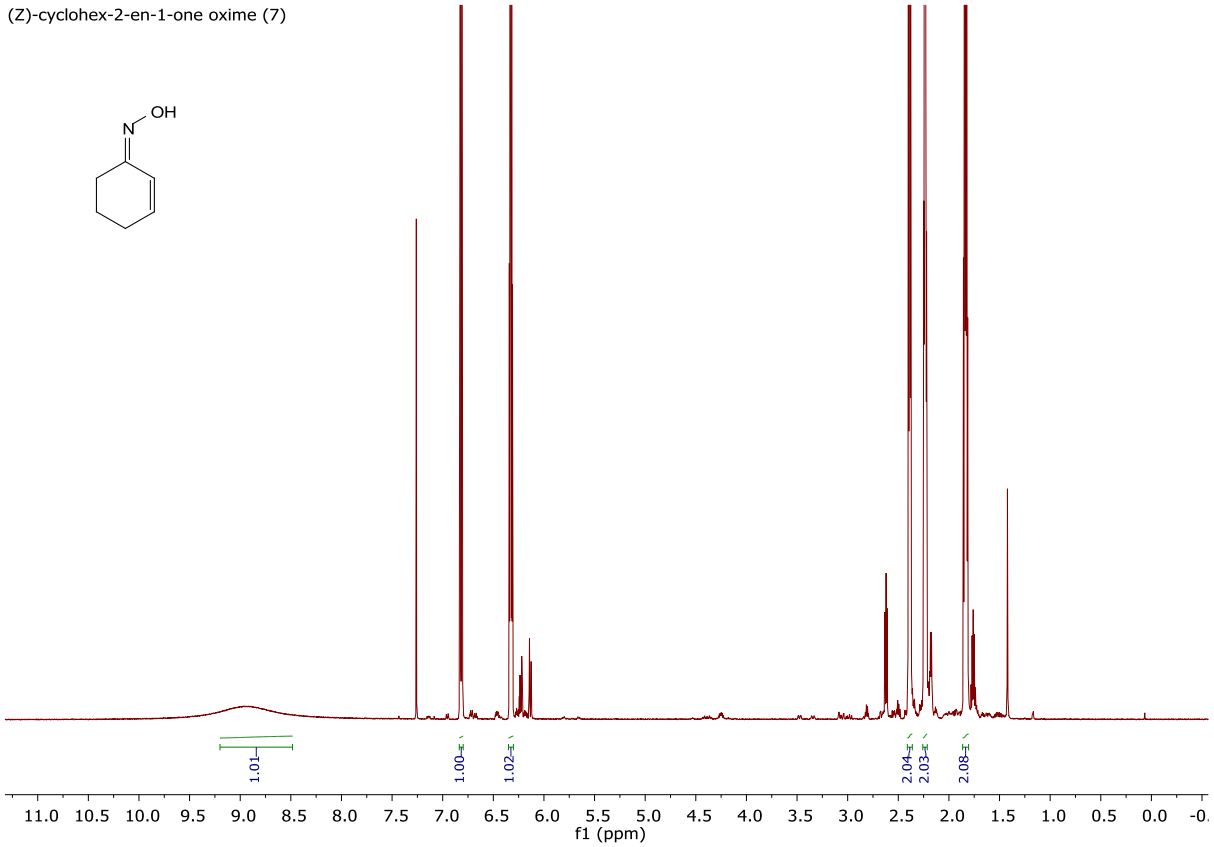
Compound **3-187a** $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$)



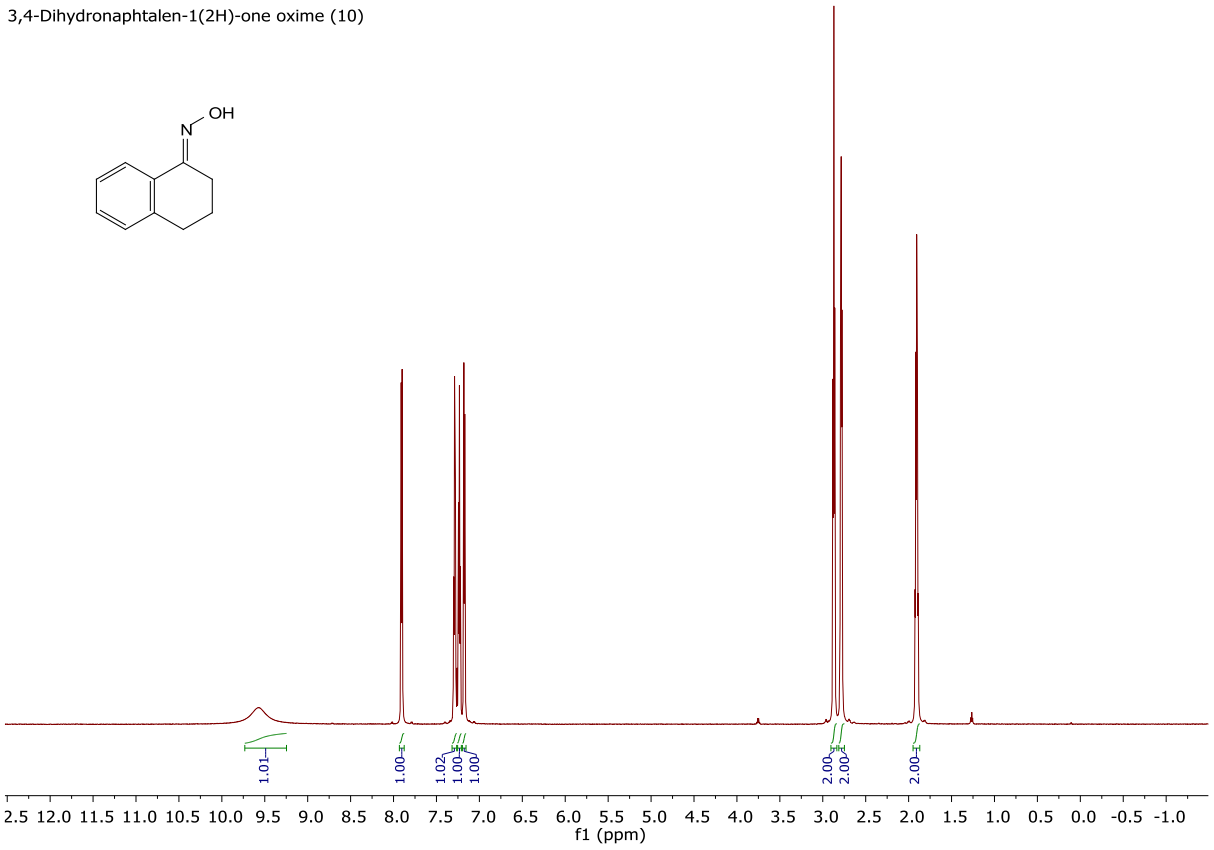
Compound 3-187 HSQC (600 MHz, $CDCl_3$)



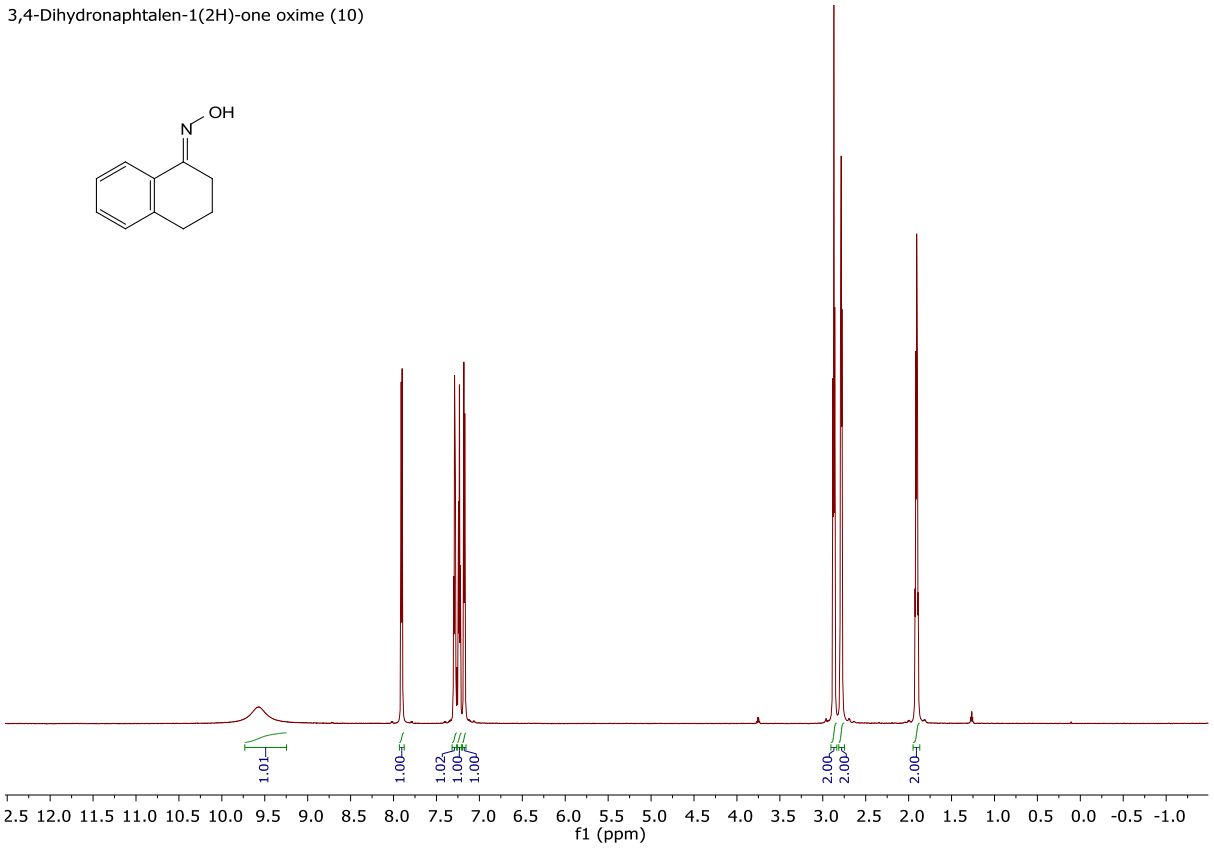
Compound 3-187b ^{1}H NMR (600 MHz, $CDCl_3$)



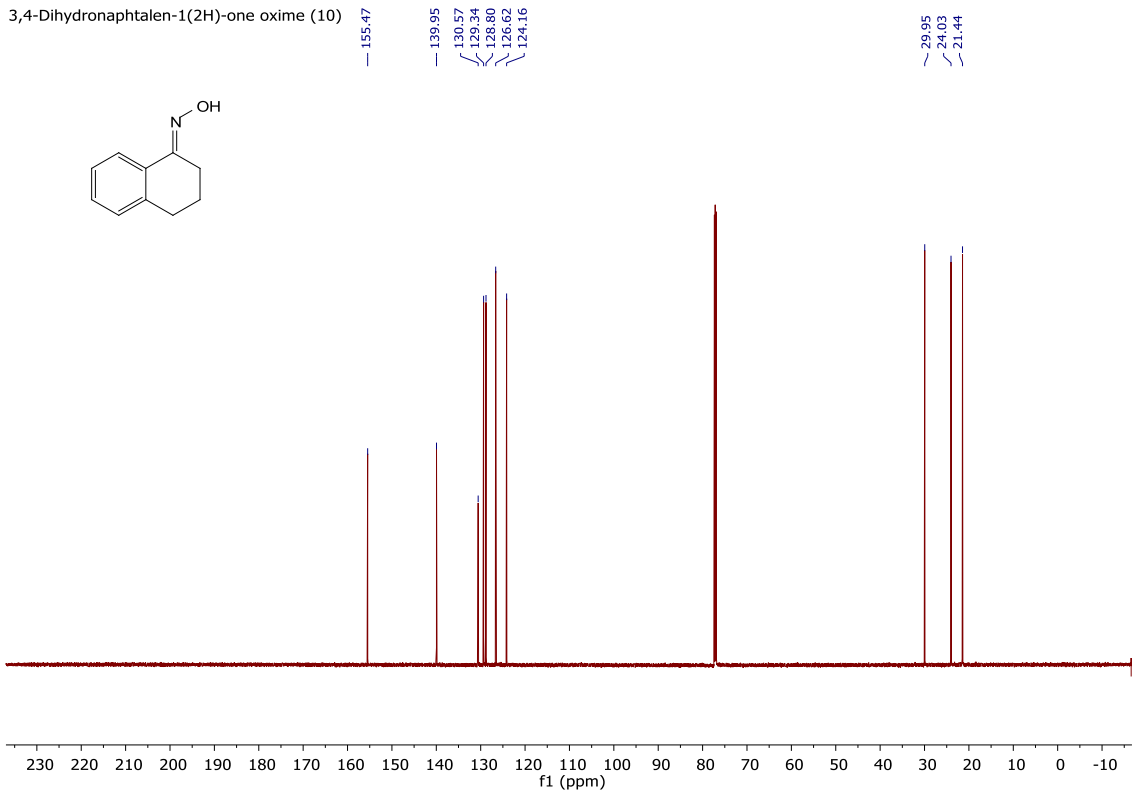
Compound **3-187b** ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$)



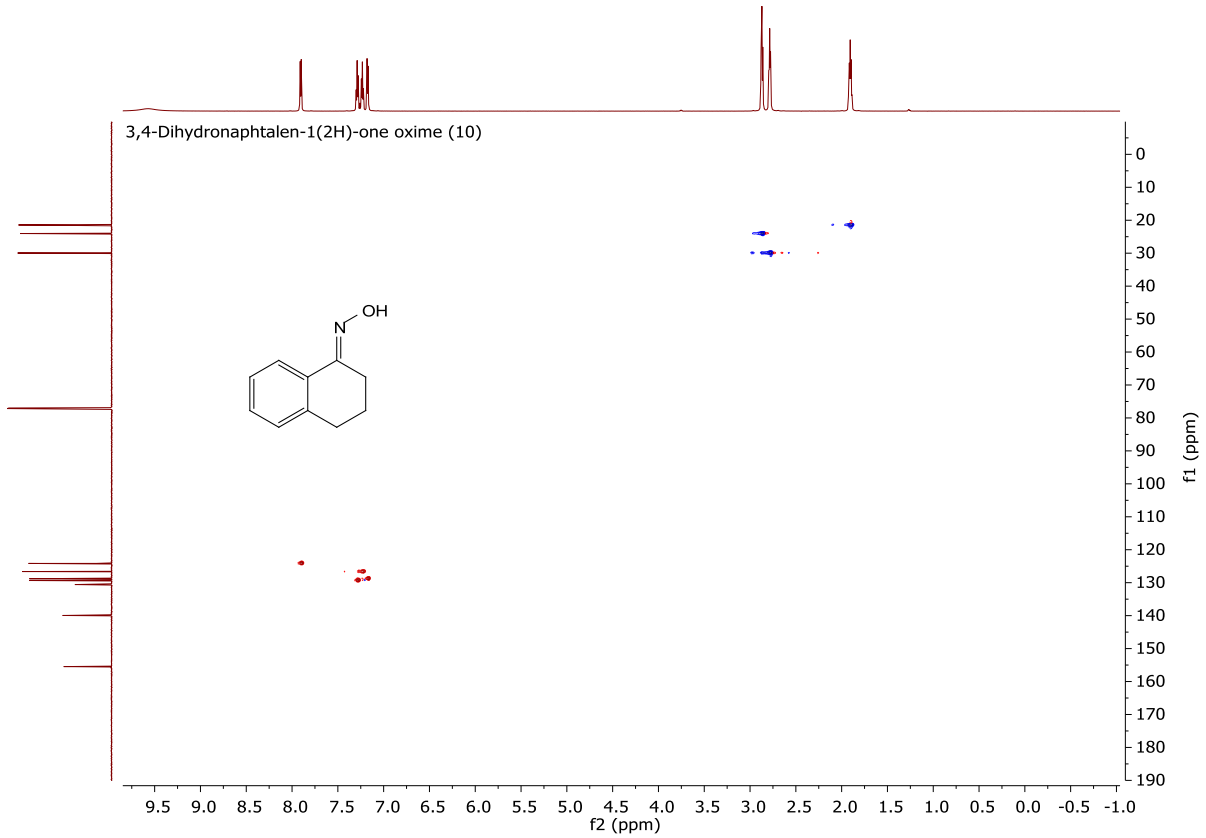
Compound 3-196b ^{1}H NMR (600 MHz, $CDCl_3$)



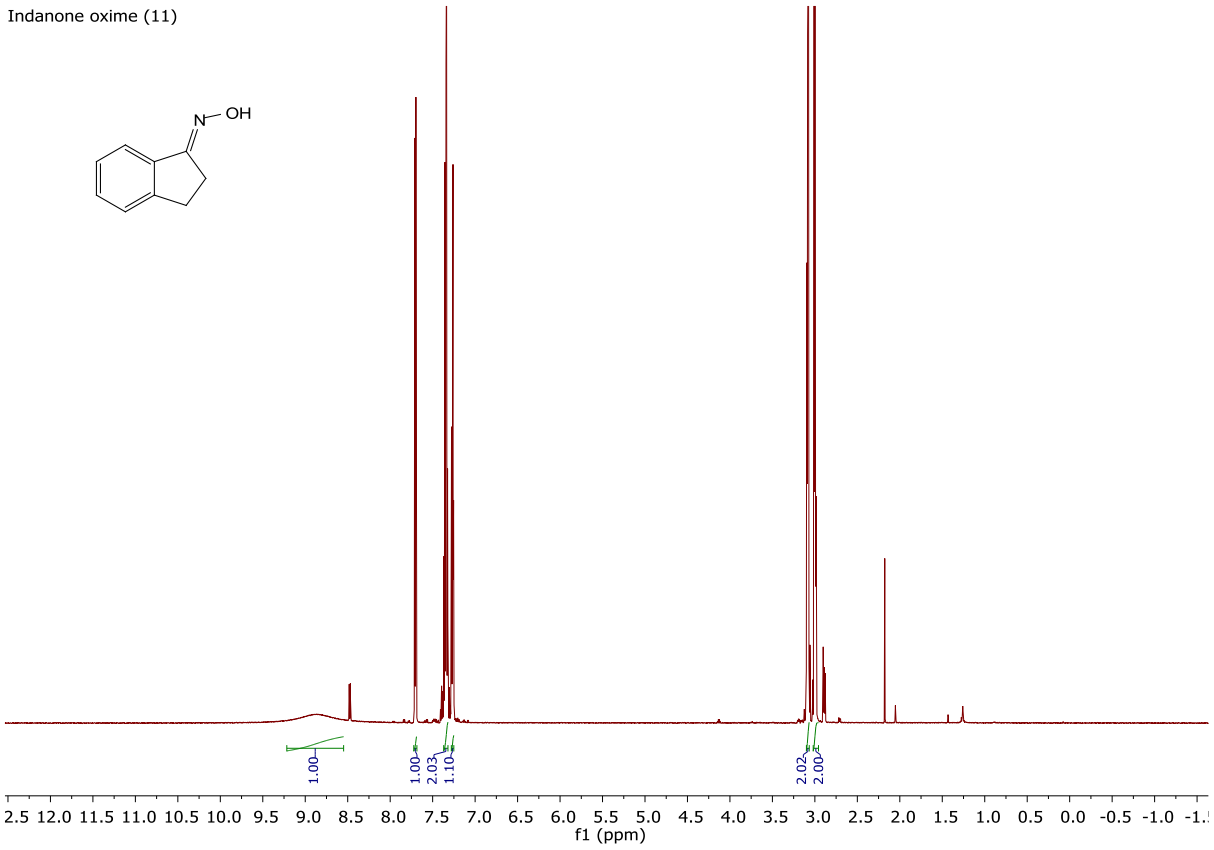
Compound **3-196b** $^{13}C\{^{1}H\}$ NMR (600 MHz, $CDCl_3$)



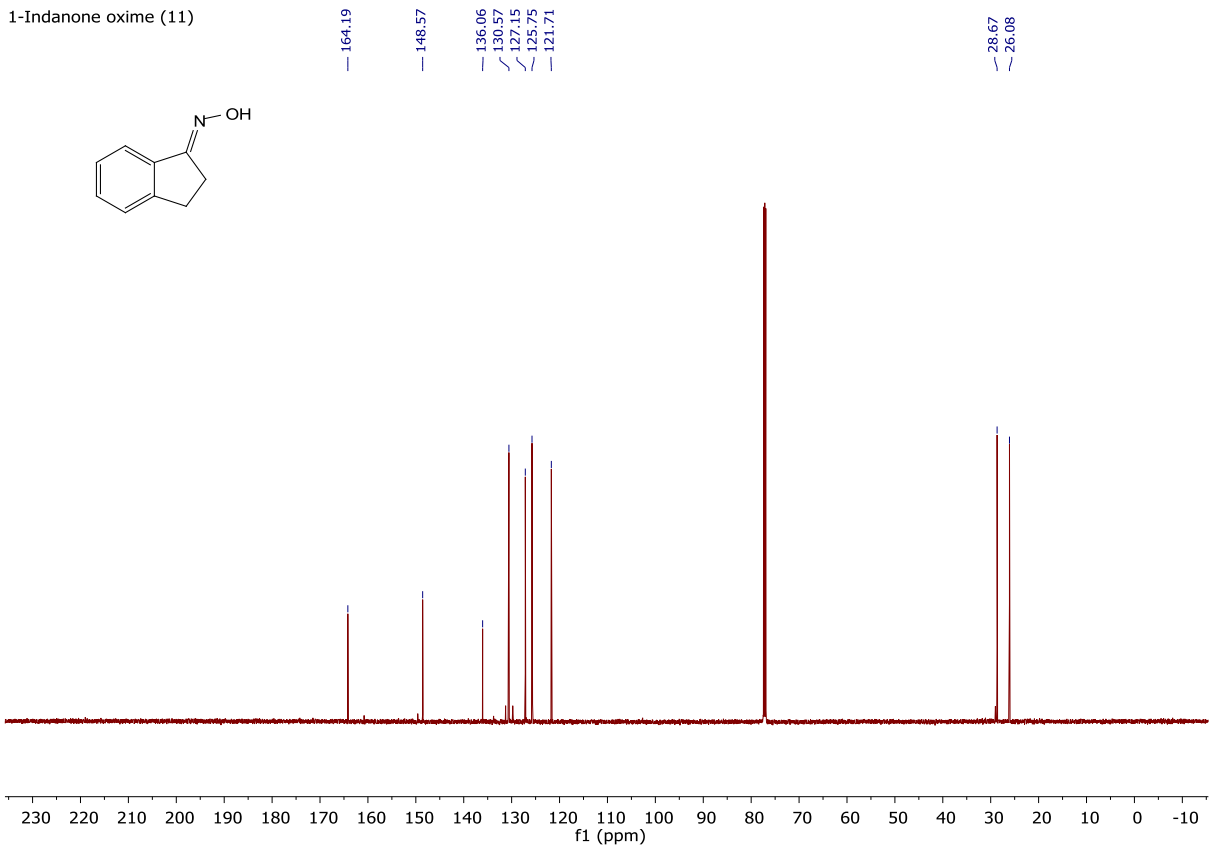
Compound 3-196 HSQC (600 MHz, $CDCl_3$)



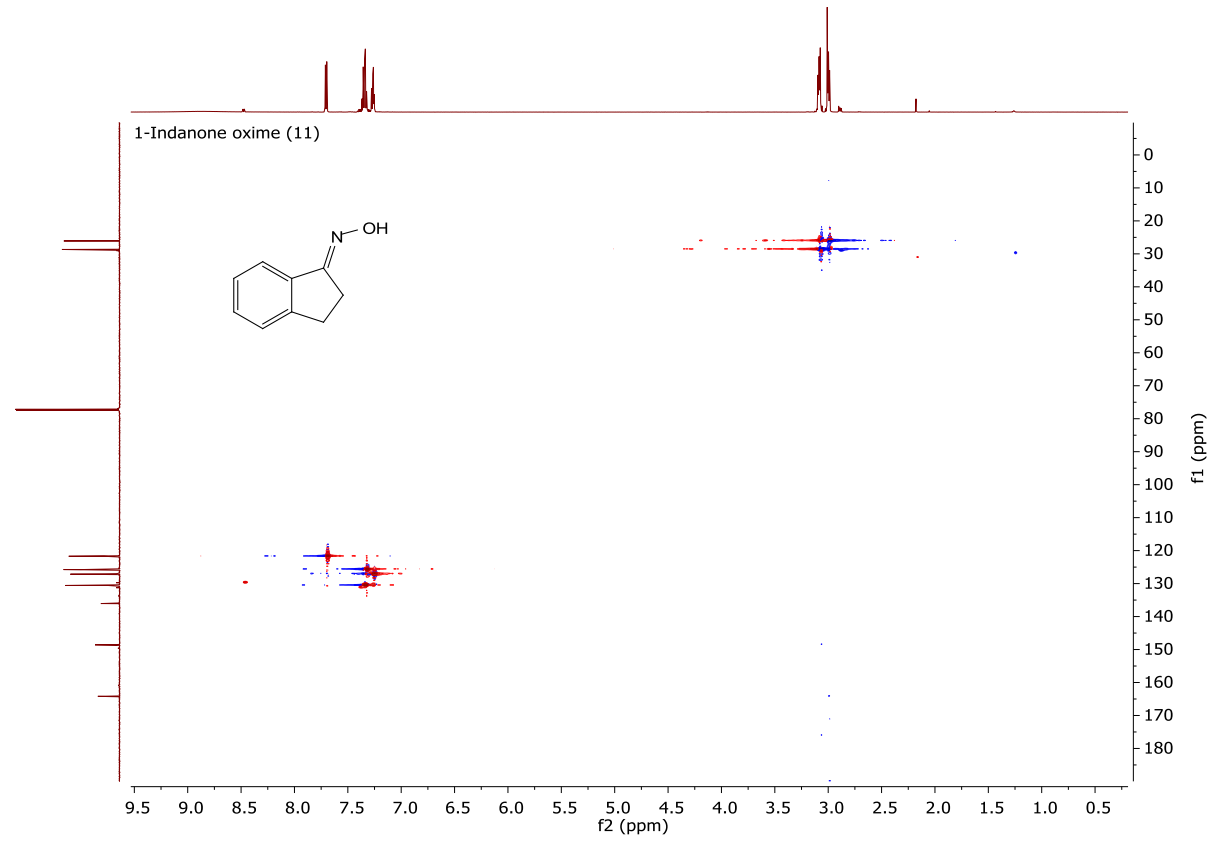
Compound 3-197b ^{1}H NMR (600 MHz, $CDCl_3$)



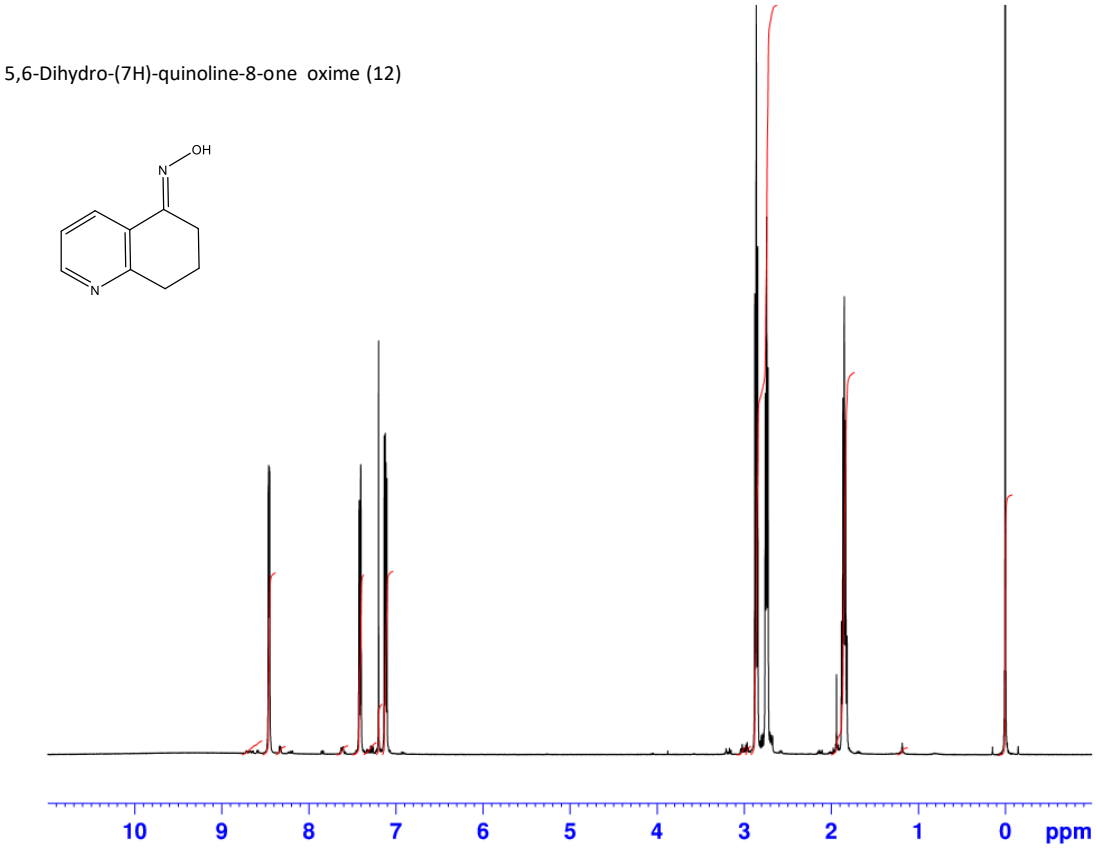
Compound **3-197b** $^{13}C\{^{1}H\}$ NMR (600 MHz, $CDCl_3$)



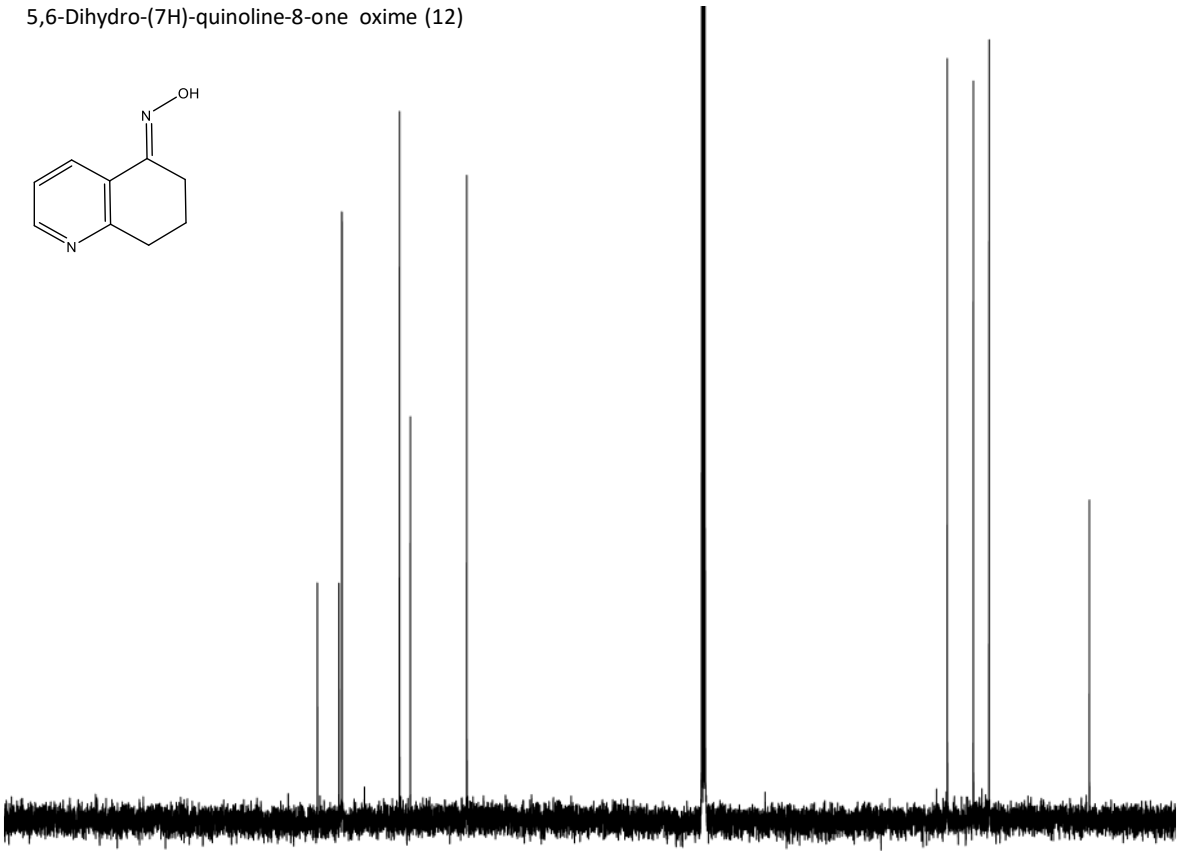
Compound 3-197 HSQC (600 MHz, $CDCl_3$)



Compound 3-198 ^{1}H NMR (600 MHz, $CDCl_3$)

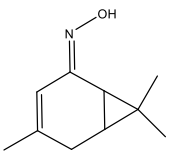


Compound 3-198 ^{13}C{^{1}H} NMR (600 MHz, $CDCl_3$)

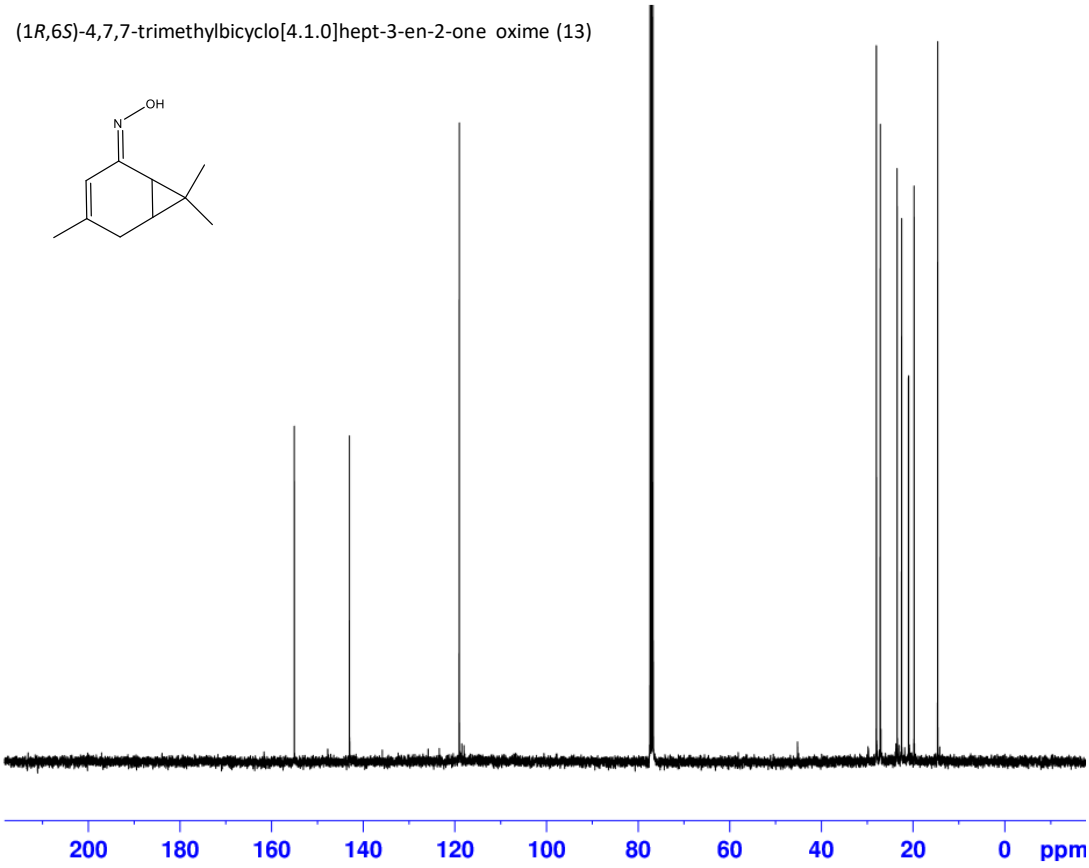


Compound 3-199 ^{1}H NMR (600 MHz, $CDCl_3$)

(1*R*,6*S*)-4,7,7-trimethylbicyclo[4.1.0]hept-3-en-2-one oxime (13)

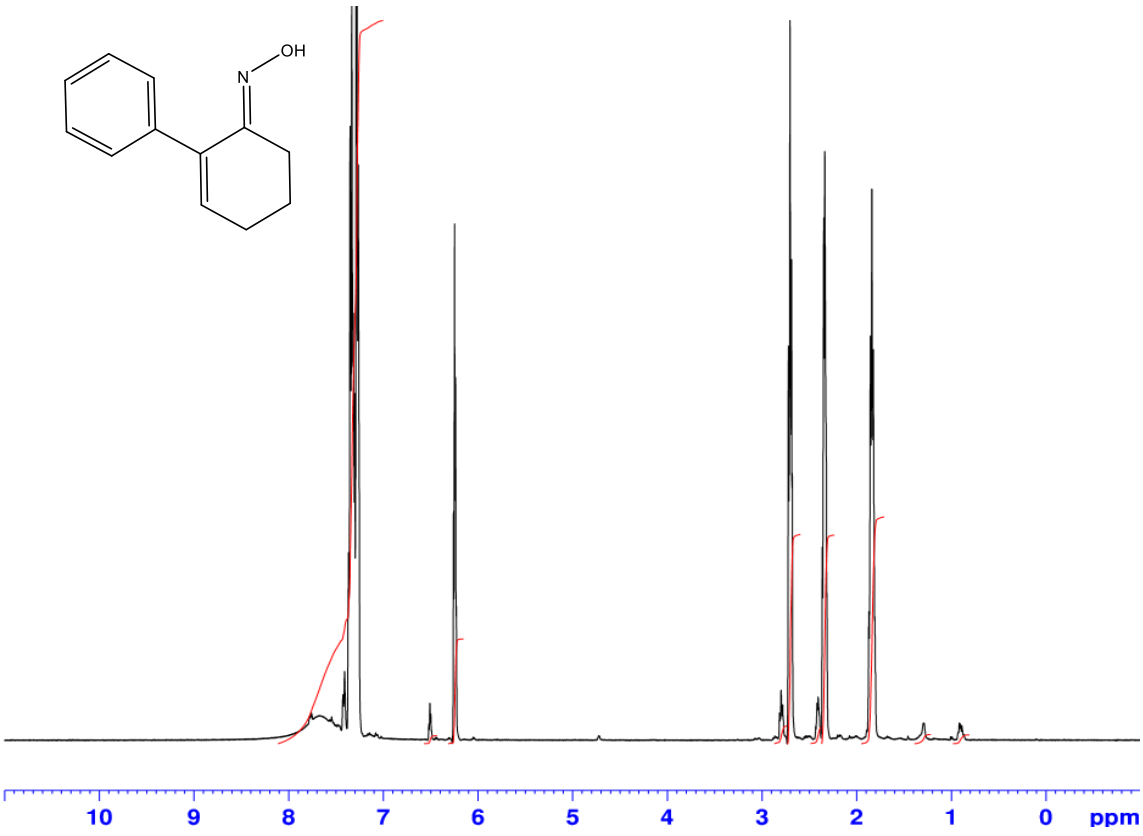


Compound **3-199** $^{13}C\{^{1}H\}$ NMR (600 MHz, $CDCl_3$)



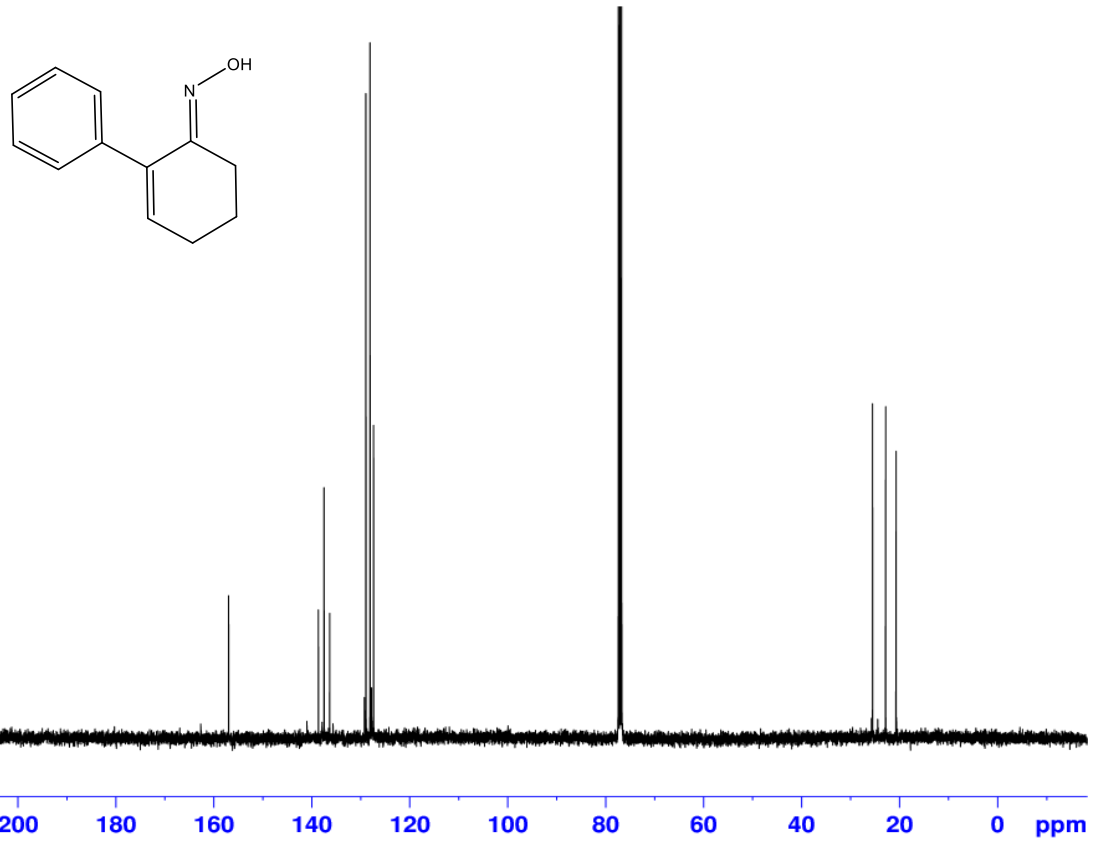
Compound 3-200 ^{1}H NMR (600 MHz, $CDCl_3$)

(E)-2-phenyl-2-cyclohexen-1-one oxime (14)



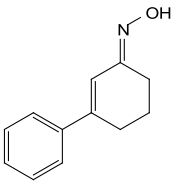
Compound **3-200** $^{13}C\{^{1}H\}$ NMR (600 MHz, $CDCl_3$)

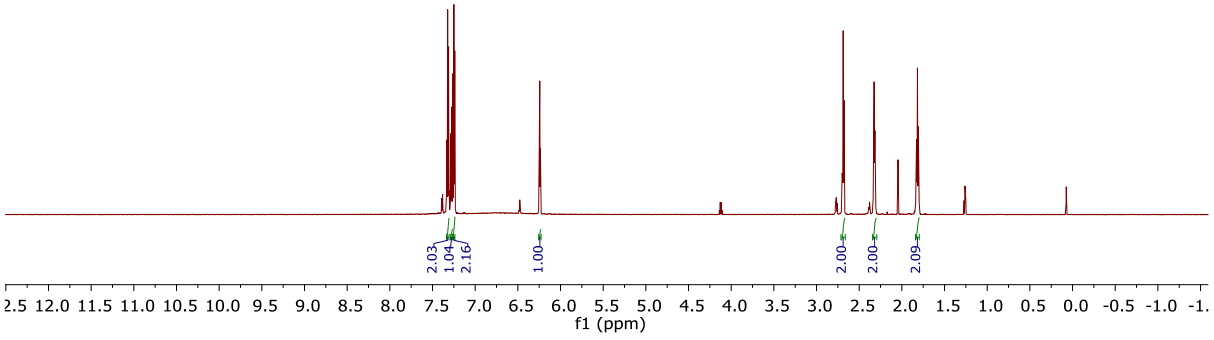
(E)-2-phenyl-2-cyclohexen-1-one oxime (14)



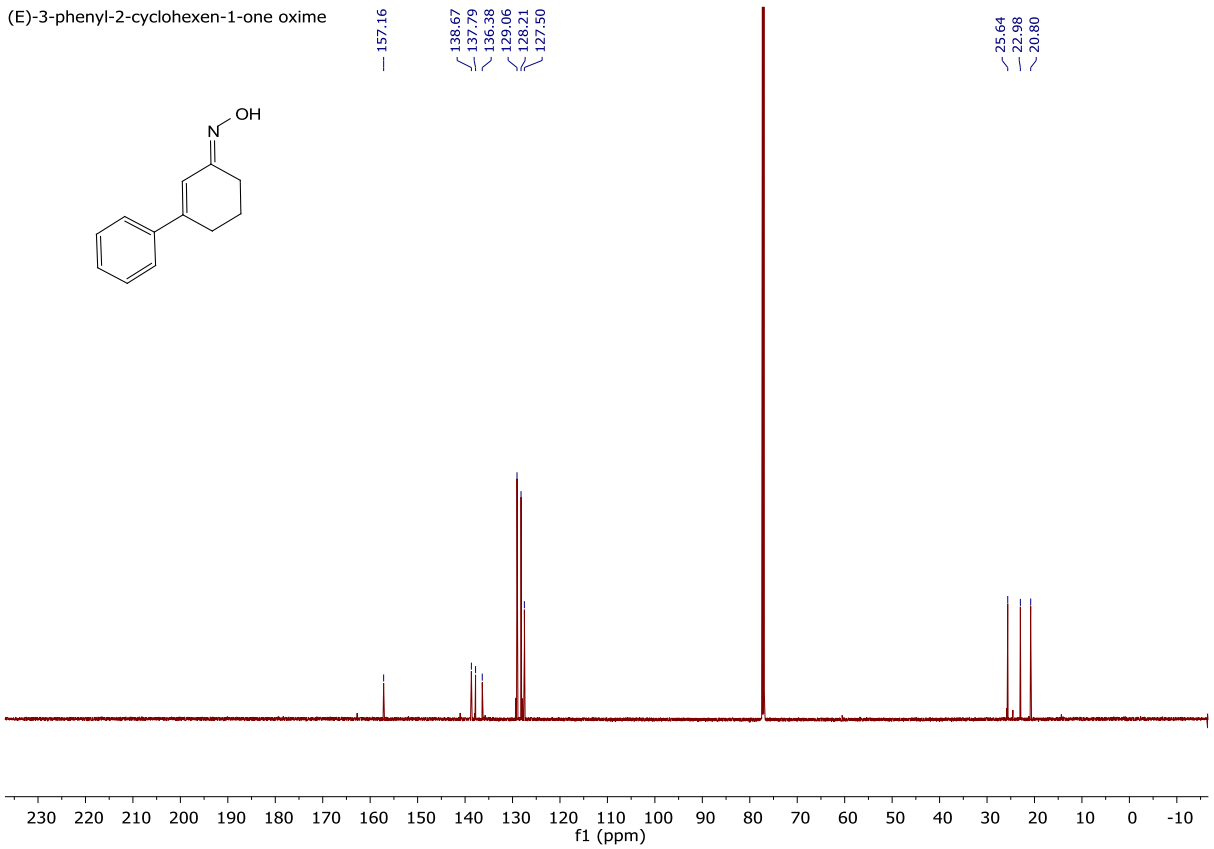
Compound 3-201 ^{1}H NMR (600 MHz, $CDCl_3$)

(E)-3-Phenyl-2-cyclohexen-1-one oxime (15)





Compound **3-201** $^{13}C\{^{1}H\}$ NMR (600 MHz, $CDCl_3$)



Compound 3-201 HSQC (600 MHz, $CDCl_3$)